The Journal of Allergy

VOL. 12 NOVEMBER, 1940 NO. 1

Original Articles

CHOLINESTERASE IN THE BLOOD OF ALLERGIC PATIENTS

ROLAND C. HAWES, B.S., AND GORDON A. ALLES, PH.D.
LOS ANGELES, CALIF.

THERE is strong evidence that the acetylcholine ion acts as a humoral agent for transference of impulses from the endings of cholinergic nerve fibers to both smooth and striated muscle, as well as at the synapses between fibers within ganglia.[1] The intensity, duration, and extension of its action appears to be limited largely by the rate of its hydrolysis into choline and acetic acid by enzymes ("cholinesterases") which are found in varying amounts in tissues and blood.

One of the commonly accepted theories of the mechanism of the asthmatic attack is that it results from constriction of the bronchial muscles consequent to reflex vagal stimulation.[2] Dixon and Brodie showed in 1903, by means of plethysmograph tracings of lung volumes of decerebrate animals which had recovered from the anesthetic, that marked bronchial constriction occurred on stimulation of the isolated vagus and on stimulation of the central end of the cut sympathetics or of certain nasal areas in animals with intact vagus nerves.[3, 4] Stimulation of the skin, stomach, or intestines failed to produce any bronchconstrictor effect. These findings are representative of many similar experiments which constitute the principal experimental support for the theory; they have not been generally confirmed in humans, however, and, as Walzer[5] points out, there are several objections to the universal acceptance of this theory of the mechanisms of the asthmatic attack.

It has also been suggested[6] that asthmatic patients as a group are vagotonic, or suffer autonomic imbalance. We are not aware, however, of the existence of any clear objective evidence tending to prove this point.

We have considered the possibility that, if a parasympathetic hyperexcitability were present in an allergic person, it might be caused by, or reflected in, an alteration of the content of the cholin-

From the laboratories of Dr. George Piness and Dr. Hyman Miller.

esterases in the blood, since the parasympathetics are cholinergic nerves. We have accordingly titrated the cholinesterase activity of the whole blood of allergic and of presumably normal persons. We have also made repeated titrations on two asthmatic patients before, during, and after acute attacks of asthma.

The method of assay used is described elsewhere.[7] It is an adaptation of the method of Stedman[8] and consists simply of mixing the blood and a solution of acetylcholine iodide in a temperature-controlled vessel, and of maintaining the pH at 7.40 ±0.10 by means of small additions of 0.02 N NaOH solution. The amount of NaOH solution required to neutralize the acetic acid liberated by the hydrolysis of acetylcholine ion for a definite period of time is proportional to the enzyme content of the blood. In conformity with the Stedman procedure, the results ("rates") are calculated as milliliters of 0.0200 N NaOH required in twenty minutes by the enzymes of 0.200 ml. of blood acting on the substrate under the conditions of assay (0.400 millimols of acetylcholine ion in a total volume of 25 ml. at 37° C. and pH 7.4). A blank of 0.085 ml. is subtracted to allow for the hydrolysis of the acetylcholine ion by the hydroxyl ions present.

The accuracy of titration, the justification of the experimental methods used, and the hazards of interpretation of the data are considered in detail in the reference cited.[7] Allergic patients were selected from the office and clinic patients of Dr. George Piness and Dr. Hyman Miller, who cooperated in providing diagnoses. Normal bloods were obtained from ambulatory patients and staff members of the orthopedic clinic of the Cedars of Lebanon Hospital, Los Angeles.

For the purpose of determining whether observations, taken individually or in groups, are significantly different from one another, there are available accepted methods that are applicable to small samples, which serve to standardize the procedure and the results.[9] The symbols "s" and "i" in the tables represent the estimates from the samples of the standard deviation of the distribution and of the index of variation, respectively. The "i" is found by dividing "s" by the arithmetical mean of the observations, and it is useful in comparing the variation of samples whose means differ appreciably.

RESULTS OF CHOLINESTERASE TITRATIONS

In order to have a basis for comparison of our results on allergic persons, we made measurements of whole blood cholinesterase activity in twenty-five normal persons, and we followed four of these for about four months to learn of the extent of variation to be expected in a single person. The results are given in Tables I and II. In Table I the data are subdivided according to sex, and further into age groups of 0 to 9, 10 to 19, 20 to 34, 35 to 49, and 50 years and older. No significant sex or age differences are observable.

TABLE I

TITRATIONS IN NORMAL PERSONS

MALES			FEMALES		
PERSON	AGE	RATE	PERSON	AGE	RATE
E. V.	14	0.501	V. K.	26	0.792
			M. K.	26	0.748
			M. A.	32	0.747
B. W.	34	0.947	C. F.	24	0.716
C. B.	29	0.846	L. F.	23	0.735
C. C.	24	0.670	P. G.	22	0.542
R. W.	30	0.821	F. B.	25	0.633
D. F.	25	0.700	R. L.	24	0.805
Mean of Group		0.797	Mean of Group		0.714
G. A.	36	0.780			
H. M.	40	0.902	E. J.	38	0.714
G. P.	46	0.876	G. W.	35	0.895
F. K.	36	0.633	C. S.	45	0.986
P. K.	35	0.724			
Mean of Group		0.783			
G. M.	66	0.554	S. R.	58	0.803
S. M.	52	0.934	Y. R.	66	0.919
Mean of Males		0.761	Mean of Females		0.772
s		0.144	s		0.118
Mean of Normal Persons		0.766			
s		0.129			

TABLE II

TEMPORAL VARIATION OF ENZYME

BLEEDING DATE	RATES			
	B. W. (MALE) AGE 34	E. J. (FEMALE) AGE 38	V. K. (FEMALE) AGE 26	M. K. (FEMALE) AGE 26
9/21/36	0.865			
10/ 5/36	0.967	0.736	0.785	0.703
10/ 6/36	0.918	0.714	0.736	0.735
10/ 7/36	0.971	0.687	0.838	0.763
10/ 9/36	0.910	0.698	0.825	0.724
10/10/36	1.000		0.788	0.737
10/13/36	0.968	0.810	0.793	0.805
10/20/36	0.915	0.705	0.765	0.710
10/27/36	0.981	0.702	0.822	0.814
11/ 3/36	0.911	0.736	0.754	0.720
11/13/36	0.931		0.754	0.746
11/25/36	0.960	0.704	0.803	0.750
12/14/36			0.834	0.739
12/17/36	0.965	0.652		
1/30/37	0.994	0.707	0.805	0.777
Means	0.9469	0.7137	0.7923	0.7479
s values	0.034	0.038	0.048	0.044
i values	0.036	0.053	0.061	0.059

The variation in any one person from time to time appears, from the small number of persons tested, to amount to about one-third of that found between different persons.

Titrations were made in the blood of forty-six definitely allergic persons. The results are shown in Table III, divided by age and sex as

TABLE III

TITRATIONS IN ALLERGIC PATIENTS

MALES			FEMALES		
PERSON	AGE	RATE	PERSON	AGE	RATE
R. D.*	6	1.033	J. A.	9	0.870
G. S.*	7	0.556	B. A.	8	0.837
A. Z.*	8	0.876	E. T.*	7	0.862
L. G.*	8	0.912	L. K.*	6	0.755
E. D.*	8	0.716	Mean of Group		0.831
E. B.*	7	0.932			
W. G.*	6	0.790			
V. W.	9	0.917	E. E.*	11	0.775
D. V.*	6	0.801	K. J.	10	1.063
R. L.*	8	0.798			
Mean of Group		0.833			
J. F.*	17	0.982	W. B.*	32	0.993
L. B.*	18	0.745	E. W.*	25	0.615
J. A.	10	0.710	C. S.	32	0.713
E. I.*	10	0.836	H. H.	23	0.931
Mean of Group		0.818	B. L.*	20	0.780
			Mean of Group		0.806
R. B.	24	0.859	F. B.	42	0.645
G. D.*	31	0.860	E. L.*	35	1.068
R. H.	28	0.549	F. M.	39	0.866
			D. G.	48	0.668
L. F.*	39	0.815	E. J.	48	0.791
D. B.	40	0.799	M. C.*	38	0.718
J. H.*	39	0.795	V. R.	41	0.658
H. O.	37	0.555	L. P.	35	0.711
C. B.*	42	0.735	E. W.*	43	0.674
			G. C.*	43	0.655
Mean of Group		0.740	R. L.	50	0.676
J. S.	59	0.727	Mean of Group		0.739
G. D.*	64	0.812			
Mean of Males		0.796	Mean of Females		0.787
s		0.124	s		0.134
Mean of Allergic Patients 0.792					
s 0.127					

*Asthmatic.

TABLE IV

TEMPORAL VARIATION OF ENZYME IN ALLERGIC PATIENTS

BLEEDING DATE	RATES				
	R. B. (MALE) AGE 24	L. F. (MALE) AGE 39	G. D. (MALE) AGE 31	J. S. (MALE) AGE 59	F. B. (FEMALE) AGE 42
10/19/36	0.844	0.872	0.868	0.739	0.652
10/20/36	0.887		0.869	0.728	0.632
10/21/36	0.815	0.813	0.800	0.701	0.649
10/22/36	0.872		0.851	0.741	0.660
10/23/36	0.877	0.771	0.869		0.633
10/26/36		0.804	0.904		
Mean	0.859	0.815	0.860	0.727	0.645
s value	0.024	0.039	0.041		0.012
i value	0.028	0.048	0.048		0.019

before. Also, five of them were followed for one week (Table IV). Most of these patients had received treatment, and none were having severe symptoms at the time of bleeding. Those whose principal complaint was asthma are marked. A separate compilation of the results for the asthmatic patients showed results practically identical with the others. As before, no age or sex difference was found.

A comparison of Tables I and III shows that allergic patients do not differ from normal persons in regard to the activity of their whole blood cholinesterases as measured by our method.

TABLE V

TITRATIONS IN ASTHMATIC PATIENTS DURING ATTACKS (NOV. 9, 1936)

PATIENT	TIME									
	3 P.M.	5 P.M.	8 P.M.	9 P.M.	11 P.M.	9 A.M.	2 P.M.	7 P.M.	10 P.M.	9 A.M.
W. B.	1.05	1.05	1.01*	1.01*	1.03*	1.06	1.06	1.01	1.01	0.90
E. W.	0.66	0.64	0.69		0.67*	0.64	0.68	0.69	0.70†	0.67

*Taken during attack.

†Attack during night. Sample taken at 3 A.M. during attack lost through technical error.

In Table V are shown the results of repeated titrations on two adult female patients who were having frequent asthmatic attacks and who were hospitalized for observation. It can be seen that there was no abnormal change in the enzymes before, during, or after the attacks, which were typical in severity and duration.

CONCLUSIONS

Titrations by a highly precise method of the activity of whole blood enzymes in splitting acetylcholine ion showed no difference between normal and allergic persons, even during attacks of asthma.

The results confirm the reports of others in showing a relatively wide range of variation of normal values and no sex or age differences.

REFERENCES

1. Brown, G. L.: Physiol. Rev. **17:** 485, 1937.
2. Bray, G. W.: Recent Advances in Allergy, Philadelphia, 1931, P. Blakiston's Son & Co., p. 21.
3. Dixon, W. E.: M. J. & Rec. **130:** 576, 1929.
4. Dixon, W. E., and Brodie, T. G.: J. Physiol. **29:** 97, 1903.
5. Walzer, M. W.: Practice of Medicine, Tice, New York, W. F. Prior Co., Inc., vol. V.
6. Eppinger, H., and Hess, L.: Ztschr. f. klin. Med. **67:** 345, 1909.
7. Alles, G. A., and Hawes, R. C.: J. Lab. & Clin. Med. To be published.
8. Stedman, E., Stedman, E., and Easson, L. H.: Biochem. J. **26:** 2056, 1932.
9. Fisher, R. A.: Statistical Methods for Research Workers, London, 1932, Oliver and Boyd.

QUANTITATIVE MEASUREMENT OF WHEALING IN HYPERSENSITIVENESS TO COLD TREATED WITH HISTAMINE AND HISTAMINASE

FRED E. MAISEL, M.D., AND HAROLD A. ABRAMSON, M.D.
NEW YORK, N. Y.

RECENT studies[1] have indicated that certain persons who respond to ordinary variations of low temperatures by whealing may be treated successfully by the administration of histamine and histaminase. In the cases thus far reported, the success of the treatment apparently has not been evaluated by quantitative measurement of the whealing response as determined by the height of the wheal after treatment. A case of hypersensitiveness to cold has been treated with histamine and histaminase by the authors. The response to whealing was measured by a contour gauge[2] particularly constructed for the quantitative measurement of the rate of wheal formation in the human skin. In addition, a simple device was employed to apply cold to the skin of the patient under standard conditions. The patient treated received a total of 50 mg. of histamine and 525 units of histaminase without any effect upon the response of the skin by whealing to stimulation by cold.

METHODS

The contour gauge used to measure the rate of wheal formation has been described previously by Abramson and Gorin.[2] It consists of square pencil leads which are mounted vertically to permit freedom of movement in a vertical direction. A fairly flat area of the skin is chosen and marked to obtain a base line. To follow the subsequent whealing in the course of the experiment, the pencil leads can be moved freely perpendicular to the skin so that the contour of the skin at the site of measurement may be recorded as a function of time.

Cold (ice) was applied to the patient's skin by means of a test tube having for its base a one-cent piece which was filed smooth and cemented to the test tube. This was filled with finely cracked ice and applied for five minutes to the skin of the forearm whenever a cold stimulus was required. The cold transmission was through the metal base.

CASE REPORT

The patient studied was a Puerto Rican woman, 51 years old, who, following her menopause at the age of 46, had noticed symptoms of chronic bronchitis, asthma, and urticaria. Her asthmatic attacks occurred at irregular intervals and were intensified on partaking of cold drinks. Urticaria was observed on the parts of her

From the Medical Service of Dr. George Baehr and the Laboratories of Mount Sinai Hospital, New York, and the Biological Laboratory, Cold Spring Harbor, Long Island.

body (face and hands) which were exposed to cold, although the asthma and urticarial response to cold did not necessarily occur simultaneously.

The patient had a past history of filariasis (febrile), and while under observation, she had two febrile episodes associated with redness and pain in the affected leg. There was no family history of allergy. On physical examination, there were diffuse sibilant and sonorous râles. The right leg was swollen with a slight pitting edema.

Intradermal tests to the usual routine series of allergens were negative, although dermographism interfered with the readings. The white blood count was 10,500, with 7 per cent eosinophiles.

In the winter months of 1938, it was easily observed that the patient responded by whealing to the cold weather encountered in New York City. Her face had a cobblestone appearance after an ordinary exposure.

EXPERIMENTAL DATA

Immersion of the hands in a large volume of water at 8° C. for only thirty seconds resulted in itching of the exposed part, occurring within from one to two minutes after removal of the hands from the cold bath. Within from three to five minutes, discrete urticarial wheals appeared, with a diminution of the itching. Whealing was not observed on the palmar surface of the fingers or metacarpal area. There were no systemic reactions. The urticarial reaction occurred with exposure of the hands for thirty seconds in water having a temperature as high as 20° C. Attempts to inhibit the reaction by immediately placing the hand exposed to cold into a 45° C. bath for some length of time were unsuccessful; nor was an urticarial response prevented by treatment with water at 45° C. for a short period and subsequent exposure to water at 8° C.

Fig. 1.—Whealing response to cold before treatment following the application of a standard stimulus. The numbers refer to the age of the wheal in minutes.

Therapy by histamine was begun on April 6, 1938. In Fig. 1 the line marked zero is the base line obtained for an area of the skin before application of the cold to the forearm by the technique employing the metal-bottom test tube. The broad band marked 20 is the contour of the wheal obtained by the contour gauge after five minutes' application of cold. The height of the wheal was approximately 2.2 mm. The wheal in this patient has a broader diameter than that of the one-cent piece through which the cold was applied to the skin. We cannot state whether spreading of the wheal was due to an unusually high pressure of the whealing fluid or to the establishment of temperature gradients from the source of cold adjacent to the periphery of the base of the test tube containing the cracked ice. The wheal, illustrated in Fig. 2, shows no pseudopods, despite its unusual height and uniform spread.

According to Bray,[3] treatments for one month with a total of 15 mg. of histamine sufficed to control or prevent certain cases of cold urticaria. His technique was adopted, and treatments were begun with 0.1 mg. histamine injected subcutaneously, increasing this dose up to the point of tolerance (which was 0.5 mg. in this case). At the end of one month's treatment, application of cold and measurement of the wheal response with a contour gauge were done on the same area of the forearm originally investigated. At this time, the wheal height reached 2.0 mm. The height of this wheal was within the limits of error identical with that given in Fig. 1. There was, therefore, no diminution in either the rate of wheal formation or the size of the wheal. Treatment was continued during the summer months until Oct. 18, 1938, when the patient responded to her injection of 0.5 mg. of histamine with a severe asthmatic paroxysm. Again measurement of the whealing response to cold by the contour gauge showed that the patient's skin sensitiveness to cold was unchanged. In order to determine if the patient's response of an asthmatic attack to histamine injection was on a psychic basis, buffered saline was injected at other visits, but no reaction resulted.

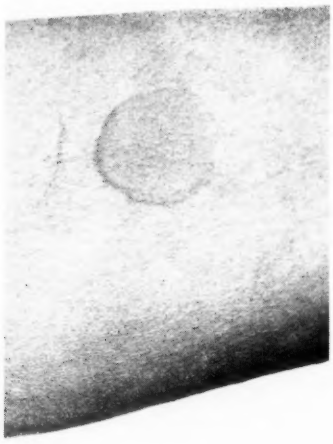

Fig. 2.—Whealing response to application of a standard cold stimulus. The actual height and width of the wheal are illustrated in Figs. 1 and 3.

Fig. 3 illustrates whealing response of this patient after she had received 50 mg. of histamine. It will be noted that a large papule remained fifty minutes after exposure to cold and that our quantitative investigation of the whealing response to cold in this patient has revealed that histamine was without any effect whatsoever. We have no explanation to offer for the failure of this patient to respond to treatment by histamine, although the filariasis may be considered a complication.

In May, 1939, histaminase treatment was started. The patient was given 5 units (in capsule) three times a day for one week, a total of 105 units. There was no effect upon the whealing response to cold. The fol-

lowing week she was given a massive dose of 120 units daily for two successive days. There was no diminution in her whealing response after taking a total of 525 units of histaminase orally. (No histaminase was available experimentally for use hypodermically.)

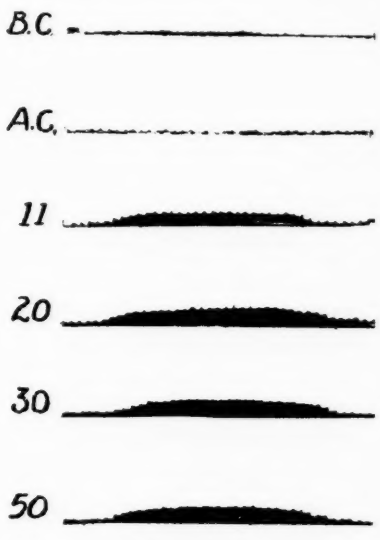

Fig. 3.—Whealing response to cold after treatment following the application of a standard stimulus. The numbers refer to the age of the wheal in minutes.

Throughout all the experiments with the cracked ice in a test tube, a similar tube weighing the same, but containing ordinary glass beads, was applied as a control, to eliminate the factor of dermographism. There was no wheal produced with the control test tube.

DISCUSSION

According to those who claim that treatment with histamine diminishes the skin sensitiveness to cold allergy, the process may be considered to be a desensitization by histamine. Indeed, the rationale of histamine therapy by desensitization is based upon the theory that histamine is liberated in this condition. If we examine the results of treatment to skin sensitiveness in other allergic conditions, as in pollinosis, it will be observed that successful clinical results with the treatment of hay fever by injection of pollen extracts is not usually accompanied by a loss of skin sensitiveness to the pollen itself. Indeed, therapy of ragweed hay fever by desensitization with histamine has not yet had a place in our conventional therapeutic armamentaria.

Since clinical improvement in pollinosis may be accompanied by no change in skin sensitiveness, it is apparent that the skin sensitiveness is not a necessary corollary of improvement. One of us (H. A. A.) has administered histamine by electrophoresis in fairly large doses for periods of more than a month with no evident change in skin sensitive-

ness to histamine. After assuming on the basis of these experiments that the administration of small amounts of histamine does not change the skin sensitiveness to histamine itself, it does not seem likely to the authors that the treatment of a condition presumably caused by histamine will necessarily respond to administration of histamine. It would appear that further clinical trial using *quantitative* methods of the type described is needed to clarify the status of histamine therapy in cases of whealing produced by application of cold.

SUMMARY

Quantitative methods are described for studying the whealing response to cold.

A case of cold urticaria was treated with graded doses of histamine and histaminase; 50 mg. of histamine and 525 units of histaminase were administered without any effect upon the size of the wheal or its rate of formation after the application of a standard cold stimulus.

REFERENCES

1. Roth, G. M., and Horton, B. T.: Proc. Staff Meet., Mayo Clinic **12**: 129, 1937.
2. Abramson, H. A., and Gorin, M. H.: J. ALLERGY **10**: 159, 1939.
3. Bray, G. W.: Proc. Roy. Soc. Med. **131**: 32, 1931.

SNAKE VENOM AND ALLERGY

HARRY G. GOLAN, M.D.
RICHMOND HILL, N. Y.

I. REACTIONS IN ALLERGIC AND NONALLERGIC PERSONS TO INTRACUTANEOUS TESTS WITH SNAKE VENOM

IT IS generally agreed that one of the outstanding characteristics of tissue response in allergy is edema and that this is the result of an increase in the permeability of the blood vessels. In the course of experimental work on Shwartzman's phenomenon, Peck[1] observed that the preparation of a site with a vascular poison such as snake venom rendered it refractory to the production of this phenomenon. The refractory state was attributed to some change in the vessel walls which made them resistant to the action of toxic filtrates and prevented hemorrhage. With this in mind, Peck employed snake venom in the treatment of diseases which were considered the result of a hemorrhagic diathesis. Favorable results were obtained in this group. As the platelet count was not materially affected by the treatment, the improvement was attributed to the direct action of the venom upon the blood vessels. Again in 1935, Peck and Rosenthal[2] reported their results of treatment with snake venom given subcutaneously in patients with two types of diseases: those without blood changes, such as idiopathic nasal bleeding, bronchiectasis with hemoptysis, functional uterine bleeding, toxic anaphylactic or endocrine purpura, and Osler's disease (multiple hereditary telangiectasis); and diseases associated with bleeding as a result of definite blood changes, such as thrombocytopenic purpura hemorrhagica and hemophilia. They concluded that in some cases, especially those of functional uterine bleeding and idiopathic nasal bleeding, there was definite improvement with this form of treatment. They found no contraindications to the therapeutic use of snake venom. In 1936, Goldman[3] reported a series of cases of recurrent epistaxis, in which moccasin snake venom was used with success, and he recommended it as an additional valuable therapeutic agent in this condition.

Peck[1] also used moccasin snake venom in the treatment of a series of thirty-two patients with allergic illnesses, such as urticaria, neurodermatitis, asthma, hay fever, etc. In the majority of instances, definite clinical improvement seemed to follow the treatment. This use of snake venom in treating various types of hemorrhagic diathesis, as well as its possible application in certain types of allergic conditions, seemed to warrant further investigation of the properties of snake venom in rela-

From the Allergy Divisions of the Jewish Hospital of Brooklyn and the Wyckoff Heights Hospital.

tion to its effect on capillary permeability. The writer was particularly interested in this problem in its possible relationship to the field of allergy.

It seemed of primary importance at the outset to compare the cutaneous responses in allergic and nonallergic persons to intracutaneous injections of moccasin snake venom. Peck, Rosenthal, and Erf,[4] in 1936, had described the intracutaneous test with moccasin snake venom as an index of prognosis in the course of thrombocytopenic purpura. Neither these writers nor their successors had entered upon any extensive studies of the reactivity of the skin in allergic persons to stimulation with moccasin snake venom.

Direct skin tests with moccasin snake venom were performed upon 50 allergic and 40 nonallergic persons. One-tenth of a cubic centimeter of a 1:3,000 dilution was introduced intracutaneously.

The reactions consisted primarily of three components—an area of hemorrhage, in the center of a wheal, which in turn was surrounded by an erythema. This reaction was described in detail by Peck.[4] Readings were taken one-half hour after the test, and the actual measurements of the three components of each reaction were recorded. The findings in the allergic and normal subjects are tabulated in Tables I, II, and III.

TABLE I

COMPARATIVE SIZES OF HEMORRHAGIC AREAS IN THE REACTIONS OF ALLERGIC AND NONALLERGIC SUBJECTS TESTED WITH SNAKE VENOM

DIAMETER OF HEMORRHAGE (CM.)	ALLERGIC SUBJECTS (50)		NONALLERGIC SUBJECTS (40)	
	NUMBER OF CASES	PERCENTAGE OF CASES	NUMBER OF CASES	PERCENTAGE OF CASES
0	0	0	1	2.5
0.1-0.4	9	18	5	12.5
0.5-0.9	41	82	34	85.0

TABLE II

COMPARATIVE SIZES OF WHEALS IN THE REACTIONS OF ALLERGIC AND NONALLERGIC SUBJECTS TESTED WITH SNAKE VENOM

DIAMETER OF WHEAL (CM.)	ALLERGIC SUBJECTS (50)		NONALLERGIC SUBJECTS (40)	
	NUMBER OF CASES	PERCENTAGE OF CASES	NUMBER OF CASES	PERCENTAGE OF CASES
1.0-1.4	9	18	11	27.5
1.5-1.9	29	58	24	60.0
2.0-2.4	8	16	5	12.5
2.5-2.9	3	6	0	0
3.0	1	2	0	0

It is apparent from an analysis of Table I that allergic and nonallergic subjects respond equally in the degree of local hemorrhage which they develop when tested intracutaneously with moccasin snake venom. Neither the allergic nor the nonallergic persons responded with hemorrhagic reactions as large as 1 cm. in diameter, thus excluding them from the category of hemorrhagic diathesis.

TABLE III

COMPARATIVE SIZES OF ERYTHEMATOUS AREAS IN THE REACTIONS OF ALLERGIC AND NONALLERGIC INDIVIDUALS TESTED WITH SNAKE VENOM

DIAMETER OF ERYTHEMA (CM.)	ALLERGIC SUBJECTS (50)		NONALLERGIC SUBJECTS (40)	
	NUMBER OF CASES	PERCENTAGE OF CASES	NUMBER OF CASES	PERCENTAGE OF CASES
0	6	12	17	42.5
1.0-1.9	2	4	1	2.5
2.0-2.9	4	8	5	12.5
3.0-3.9	22	44	9	22.5
4.0-4.9	12	24	7	17.5
5.0-5.9	4	8	1	2.5

The whealing reaction as a result of the intracutaneous test with snake venom appeared slightly greater in the allergic group than in the nonallergic group of subjects. The majority of wheals varied between 1.0 and 1.9 cm. in size. There were 76 per cent of such reactions in the allergic and 87.5 per cent in the nonallergic group. The remainder of the wheals varied between 2 and 3 cm. in size. Of these, 24 per cent occurred in the allergic subjects and 12.5 per cent in the nonallergic subjects. While the largest wheals (from 2 to 3 cm.) occurred exclusively in allergic subjects, their incidence was relatively small. As a whole, therefore, the difference in whealing responses between the groups was not pronounced.

The allergic and nonallergic groups also differed in degree of erythematous reaction. Twelve per cent of the allergic subjects manifested no erythematous response, whereas, 42.5 per cent of the nonallergic individuals were in this class. The majority of the erythematous reactions varied between 1.0 and 4.9 cm. in size. In the allergic group 80 per cent of the reactions were of this size. In the nonallergic group there were only 55 per cent. The remaining 8 per cent in the allergic group had erythemas varying between 5.0 and 5.9 cm. in size, whereas, in the nonallergic group there were only 2.5 per cent of such cases.

It is self-evident, therefore, that allergic subjects as a group respond with greater erythemas than do nonallergic subjects to intracutaneous tests with moccasin snake venom.

SUMMARY

A comparison of the cutaneous responses of allergic and nonallergic persons to intracutaneous tests with snake venom resulted in the following observations:

1. Allergic and nonallergic persons react equally in the degree of local hemorrhage which occurs at the center of the reactions.

2. The degree of whealing tends to be slightly greater in the allergic than in the nonallergic group.

3. The erythematous response was definitely greater in the allergic group.

4. The allergic, as well as the nonallergic, subjects gave no hemorrhage reactions reaching 1 cm. in diameter, thereby excluding them from the group of diseases based upon a hemorrhagic diathesis.

II. THE RESPONSE OF SNAKE VENOM WHEAL SITES TO RESTIMULATION WITH SPECIFIC AND NONSPECIFIC EXCITANTS

In 1935, Bowman[5] observed that, when two tests with the same solution of histamine were performed vertically 4 inches apart on the arm, the lower test gave a larger reaction in the majority of cases. The reverse was true when the same tests were done with a specific excitant, such as ragweed, upon ragweed-sensitive subjects. The above observation led Bowman and Walzer[6] to conclude that the mechanisms of the histamine reaction and the immunologic reaginic reaction were not identical. The results obtained in another of their studies[6] supported this conclusion. They observed that, when sites previously prepared by histamine or ragweed were retested subsequently with histamine or ragweed, such sites showed differences in the degree of their whealing responses. Restimulation of a histamine site with histamine after an interval of a week showed diminished permeability of the sites. On the other hand, restimulation of a histamine site with ragweed showed no diminution of the whealing reaction at the site. A ragweed site, when restimulated with ragweed, gave a whealing response slightly greater than normal. A ragweed site restimulated with histamine showed a very decided increase in the permeability of the vessels. Hence, it was evident that the nonspecific excitant (histamine) and the specific excitant (ragweed) produced different protracted effects upon the permeability of the blood vessels.

It seemed of interest to the writer to study the influence of moccasin snake venom upon the permeability of the blood vessels from this point of view. It was important to determine, if possible, whether snake venom corresponded either to histamine or to a specific excitant in its effect upon vascular permeability.

PROCEDURE

Thirty-four allergic patients were injected intracutaneously with moccasin snake venom solution. One-tenth of one cubic centimeter of a 1:3,000 dilution was injected into the anterior aspect of the forearm. After one week the same sites were again tested. At this time the remains of the initial test were still visible. A slight ecchymosis and erythema and occasionally a slight degree of induration persisted at these sites. Retests of these sites were made with an intracutaneous injection of 0.01 c.c. of a freshly prepared solution of histamine hydrochloride in a dilution of 1:10,000. A similar amount was injected into a control (normal) site. Both reactions were read

after ten minutes, and the sizes of the wheals and the erythemas were noted. The ecchymotic areas are not considered in these studies. Emphasis is laid only on the sizes of the wheals and erythemas. The comparative sizes of reactions are noted in Table IV.

TABLE IV

FIRST EXCITANT: MOCCASIN SNAKE VENOM 1:3,000
SECOND EXCITANT: HISTAMINE 0.1 MG.
(INTERVAL BETWEEN TESTS, ONE WEEK)

WHEAL LARGER ON		ERYTHEMA LARGER ON	
RETESTED SITE	CONTROL SITE	RETESTED SITE	CONTROL SITE
20.5%	79.5%	20.5%	79.5%

It is apparent that the snake venom sites, when restimulated a week later with histamine, showed a diminished permeability in almost 80 per cent of the cases. The erythematous response on snake venom sites was diminished to a similar degree.

Another group of 19 ragweed-sensitive patients were similarly injected with moccasin snake venom. One-tenth of a cubic centimeter of a 1:3,000 dilution was injected into the anterior aspect of the forearm. After one week the same sites were tested intracutaneously with a dilution of ragweed extract (specific excitant) which was capable of producing wheals of moderate size. These dilutions were determined by previous quantitative titrations of each patient's cutaneous sensitivity to ragweed. Similar tests were injected into control (normal) sites. The reactions were read after ten minutes, and the sizes of the wheals and the erythemas were recorded. The comparative sizes of the reactions on the retested and control sites are noted in Table V.

TABLE V

FIRST EXCITANT: MOCCASIN SNAKE VENOM 1:3,000
SECOND EXCITANT: RAGWEED EXTRACT
(INTERVAL BETWEEN TESTS, ONE WEEK)

WHEAL LARGER ON		ERYTHEMA LARGER ON	
RETESTED SITE	CONTROL SITE	RETESTED SITE	CONTROL SITE
57.8%	42.2%	39.5%	60.5%

It may be noted that snake venom sites, when restimulated a week later with a specific excitant, such as ragweed, were slightly more responsive in their ability to wheal than were normal sites. These same sites, however, more frequently showed a diminished erythematous response than did the controls.

DISCUSSION

Cutaneous sites on allergic subjects which had been previously prepared with moccasin snake venom, when tested a week later with his-

tamine, gave increased wheals in only 20.5 per cent (Table IV). However, cutaneous sites previously prepared with moccasin snake venom, when tested a week later with ragweed (specific excitant), gave increased wheals in 57.8 per cent of cases (Table V). The erythematous response was greater in 20.5 per cent of the sites retested with histamine (Table IV), and on sites retested with ragweed (specific excitant), in 39.5 per cent of cases (Table V). Although the size of the erythema in the latter was nearly double that in the former, it was still definitely smaller than the erythematous response on the control (normal) sites.

It is of interest to compare the above findings with those obtained by Walzer and Bowman.[6] They showed that cutaneous sites on allergic persons, previously prepared with histamine, when retested a week later with the same excitant, gave increased wheals in 20.5 per cent and increased erythemas in 14.7 per cent of the cases. Similarly, when sites previously prepared with histamine were tested a week later with a specific excitant (ragweed), they showed increased wheals in 52.5 per cent and increased erythemas in 33 per cent of the cases.

Comparison of the results obtained by Bowman and Walzer with histamine and by the writer with snake venom is given in Table VI.

TABLE VI

FIRST EXCITANT	SECOND EXCITANT	WHEAL LARGER ON RETESTED SITE	ERYTHEMA LARGER ON RETESTED SITE
Moccasin snake venom	Histamine	20.5%	20.5%
Histamine (Bowman and Walzer)	Histamine	20.5%	14.7%
Moccasin snake venom	Ragweed	57.8%	39.5%
Histamine (Bowman and Walzer)	Ragweed	52.5%	33.0%

Analysis of these figures would on first inspection seem to indicate that snake venom and histamine are alike in their effects upon the capillary permeability. This conclusion, however, is not justified, in view of the fact that snake venom and histamine differ in the degree of inflammatory reaction which follows their intracutaneous injection. Whereas, the effects of a histamine test disappear within twenty-four hours, a snake venom site still shows a considerable amount of inflammatory reaction even at the end of one week. In experiments in which this inflammatory factor could be eliminated, it was found that histamine and snake venom were not alike in their effects upon capillary permeability. This will be brought out in the following discussion.

SUMMARY

1. Cutaneous sites previously prepared with moccasin snake venom show a diminished whealing response when retested after one week with histamine, a nonspecific excitant.

2. Cutaneous sites previously prepared with moccasin snake venom show no diminished whealing response when retested after one week with ragweed, a specific excitant.

3. In both types of tests the erythematous responses were always diminished on the retested site.

III. THE WHEALING RESPONSE OF SITES PREVIOUSLY PREPARED WITH SPECIFIC AND NONSPECIFIC EXCITANTS TO RESTIMULATION WITH SNAKE VENOM

In the previous section it was shown that moccasin snake venom seemed to resemble histamine in its more lasting effects on vascular permeability. Sites prepared with moccasin snake venom, when restimulated after seven days, responded similarly to sites prepared with histamine. It was pointed out, however, that these findings might be the result of the persistent inflammatory reaction which follows the snake venom test, rather than of the initial injury itself.

Walzer and Bowman[6] had shown a difference in the results obtained with a nonspecific (histamine) and a specific (ragweed) excitant when these were used to restimulate sites previously prepared with various excitants. It seemed of interest, therefore, to determine how sites previously prepared with specific and nonspecific excitants would react to restimulation with snake venom. It would be important to determine, if possible, whether snake venom as a restimulant resembles a specific excitant, such as ragweed, or a nonspecific one, such as histamine.

PROCEDURES

Sites Prepared With Ragweed and Restimulated With Moccasin Snake Venom.—Seventeen ragweed-sensitive patients were injected intracutaneously with ragweed. The amount and concentration employed were sufficient to induce wheals of moderate size. These concentrations were determined by previous quantitative titrations of each patient's cutaneous sensitivity to ragweed. The injection was made on the anterior aspect of the arm. The following week the same sites were tested intracutaneously with snake venom. One-fiftieth of a cubic centimeter of a dilution of 1:3,000 was injected. A similar amount was injected into a control (normal) site. Both reactions were read after one-half hour, and the sizes of the wheals and the erythemas were noted. The ecchymotic areas are not reported in this paper. The comparative sizes of the reactions are recorded in Table VII.

TABLE VII

FIRST EXCITANT: RAGWEED EXTRACT
SECOND EXCITANT: MOCCASIN SNAKE VENOM 1:3,000
(INTERVAL BETWEEN TESTS, ONE WEEK)

WHEAL LARGER ON		ERYTHEMA LARGER ON	
RETESTED SITE	CONTROL SITE	RETESTED SITE	CONTROL SITE
70.5%	29.5%	32.3%	67.7%

It is apparent that ragweed (specific) sites, when restimulated a week later with snake venom, showed an increased permeability in almost 71 per cent of the cases. However, the erythematous response on the ragweed sites was diminished as compared with that on normal sites.

Sites Prepared With Histamine and Restimulated With Moccasin Snake Venom.—Twenty patients were injected intracutaneously with histamine. One-hundredth of a cubic centimeter of a freshly prepared histamine hydrochloride solution in a dilution of 1:10,000 was injected on the anterior aspect of the arm. This amount was sufficient to produce wheals of a moderate size. The following week the same sites were tested intracutaneously with moccasin snake venom. One-fiftieth of a cubic centimeter of a dilution of 1:3,000 was injected. A similar amount was injected into a control (normal) site. Both reactions were read after one-half hour, and the sizes of the wheals and the erythemas were noted. The comparative sizes of the reactions are recorded in Table VIII.

TABLE VIII

FIRST EXCITANT: HISTAMINE 1:10,000
SECOND EXCITANT: MOCCASIN SNAKE VENOM 1:3,000
(INTERVAL BETWEEN TESTS, ONE WEEK)

WHEAL LARGER ON		ERYTHEMA LARGER ON	
RETESTED SITE	CONTROL SITE	RETESTED SITE	CONTROL SITE
60%	40%	42.5%	57.5%

It is evident that histamine sites, when restimulated a week later with snake venom, showed an increased permeability in 60 per cent of the cases. However, the erythematous response on these histamine sites was diminished.

Sites Prepared With Moccasin Snake Venom and Restimulated With Moccasin Snake Venom.—Twenty-five patients were injected intracutaneously with moccasin snake venom. One-tenth of a cubic centimeter of 1:3,000 dilution was injected into the anterior aspect of the arm.

TABLE IX

FIRST EXCITANT: MOCCASIN SNAKE VENOM 1:3,000
SECOND EXCITANT: MOCCASIN SNAKE VENOM 1:3,000
(INTERVAL BETWEEN TESTS, ONE WEEK)

WHEAL LARGER ON		ERYTHEMA LARGER ON	
RETESTED SITE	CONTROL SITE	RETESTED SITE	CONTROL SITE
47.9%	45.6%	52.1%	54.4%

The following week the same sites were retested intracutaneously with moccasin snake venom. One-fiftieth of a cubic centimeter of a dilution of 1:3,000 was injected. A similar amount was injected into a control (normal) site. Both reactions were read after one-half hour, and the

sizes of the wheals and erythemas were noted. The comparative sizes of the reactions are recorded in Table IX.

From the experiments it appears that snake venom sites, when restimulated a week later with snake venom, showed a diminished permeability in 52.1 per cent of cases. The significance of the above findings will now be considered.

DISCUSSION

Cutaneous sites on allergic individuals, previously prepared with ragweed, a specific excitant, when tested a week later with moccasin snake venom, produced larger than normal wheals in almost 71 per cent of cases. It is of interest to compare the above findings with those obtained by Walzer and Bowman.[6] They showed that cutaneous sites on allergic patients previously prepared with ragweed, when tested a week later with histamine, produced wheals larger than normal in 89.8 per cent of the cases. Similarly, cutaneous sites on allergic individuals, previously prepared with ragweed, when retested a week later with ragweed, gave increased wheals in 77 per cent of cases. Comparison of the results obtained by Walzer and Bowman with ragweed and histamine tested upon sites previously prepared with ragweed, and by the writer with moccasin snake venom tested upon sites previously prepared with ragweed, may be tabulated as shown in Table X.

TABLE X

FIRST EXCITANT	SECOND EXCITANT	WHEAL LARGER ON RETESTED SITES	ERYTHEMA LARGER ON RETESTED SITES
Ragweed	Moccasin snake venom	70.5%	32.3%
Ragweed (Walzer and Bowman)	Histamine	89.8%	16.7%
Ragweed (Walzer and Bowman)	Ragweed	77.0%	17.6%

Analysis of these figures would indicate that moccasin snake venom acts more like ragweed than histamine in its restimulation of a ragweed site.

Similarly, cutaneous sites on allergic persons, previously prepared with histamine, when tested a week later with moccasin snake venom, gave larger than normal wheals in 60 per cent of the patients. It is of further interest to compare the above findings with those obtained by Walzer and Bowman.[6] They showed that cutaneous sites on allergic persons, previously prepared with histamine, when retested a week later with histamine, gave wheals larger than normal in only 20.5 per cent of the patients. Cutaneous sites on allergic persons, previously prepared with histamine, when tested a week later with ragweed, gave increased wheals in 52.5 per cent of the patients. Comparison of the results ob-

tained by Walzer and Bowman with ragweed and histamine, and by the writer with moccasin snake venom, may be tabulated as shown in Table XI.

TABLE XI

FIRST EXCITANT	SECOND EXCITANT	WHEAL LARGER ON RETESTED SITE	ERYTHEMA LARGER ON RETESTED SITE
Histamine	Moccasin snake venom	60.0%	42.5%
Histamine (Walzer and Bowman)	Histamine	20.5%	14.7%
Histamine (Walzer and Bowman)	Ragweed	52.5%	33.0%

Analysis of these figures would similarly indicate that moccasin snake venom is more like the specific excitant ragweed than like the non-specific excitant histamine in its restimulation of a histamine site.

It was shown previously that snake venom and histamine differed in the degree of inflammatory reaction which followed their intracutaneous injection. Whereas, the effects of a histamine test disappeared within twenty-four hours, those of the snake venom site still showed a considerable reaction even at the end of one week. To a degree, this factor impairs the reliability of those experiments in which moccasin snake venom is the initial excitant. A comparison of the results obtained by the writer when ragweed, histamine, or snake venom was tested upon sites previously prepared with snake venom may be tabulated as shown in Table XII.

TABLE XII

FIRST EXCITANT	SECOND EXCITANT	WHEAL LARGER ON RETESTED SITE	ERYTHEMA LARGER ON RETESTED SITE
Moccasin snake venom 1:3,000	Histamine	20.5%	20.5%
Moccasin snake venom 1:3,000	Ragweed	57.8%	39.5%
Moccasin snake venom 1:3,000	Moccasin snake venom	47.9%	52.1%

Despite the limitations of the experiment, it is again apparent that moccasin snake venom is more like ragweed than histamine in its restimulation of a moccasin snake venom site.

Although snake venom and the specific excitant ragweed show a strong resemblance in their effects upon capillary permeability and in their restimulating powers of previously tested sites, they differ in one important particular. As shown by Bowman and Walzer, a site previously stimulated with ragweed responds to a test with histamine with a wheal which is larger than normal in 89.8 per cent of the patients. On the other hand, a site previously tested with moccasin snake venom, when restimulated with histamine, responds with a wheal which is greater than normal in only 20.5 per cent. This may be accounted for, to a degree, by

the inflammatory reaction resulting from the primary skin test with the snake venom. However, this primary inflammatory reaction is not severe enough to counteract the restimulating powers of ragweed and moccasin snake venom when these are injected into moccasin snake venom sites. The evidence, therefore, seems to point to some other factor than merely the inflammatory one, which would account for failure of a snake venom site to respond to restimulation with histamine, with the same increase in the size of wheal which is obtained with histamine upon a ragweed site. This phase of the question will be subject for further study.

SUMMARY

1. Snake venom tests done on sites previously prepared with ragweed produce wheals which are larger than normal in 70.5 per cent of the patients.

2. Snake venom tests done on sites previously prepared with histamine produce wheals which are larger than normal in 60 per cent of the patients.

3. Snake venom tests done on sites previously prepared with snake venom produce wheals which are larger than normal in 47.9 per cent of the cases.

4. Snake venom tests done on sites previously prepared with any of the three excitants produce erythematous reactions which are smaller than normal in all.

5. Snake venom more closely resembles the specific excitant ragweed than the nonspecific excitant histamine in its restimulating effect upon sites previously prepared with histamine, ragweed, or snake venom.

IV. THE EFFECT OF MOCCASIN SNAKE VENOM UPON PASSIVELY SENSITIZED SITES

The experiments in sections II and III were performed on atopic patients. The method of preparing, as well as restimulating, the sites was by testing the subjects directly. At this point, it seemed of interest to the writer to study the effects of moccasin snake venom on passively sensitized sites.

Bowman and Walzer[7] showed that the whealing response of a passively sensitized site is impaired as a result of wheal formation on that site. This diminution in response is more pronounced following an immunologic (specific) wheal than a nonimmunologic (nonspecific) wheal. Such experiments were done only upon nonatopic subjects. The writer, however, conducted his experiment both upon atopic and nonatopic subjects.

Twelve normal nonatopic persons were each sensitized at two cutaneous sites with a cottonseed serum of high reaginic titer. This serum

was obtained from a patient markedly sensitive to cottonseed. The following week 0.05 c.c. of moccasin snake venom in a dilution of 1:3,000 was injected intracutaneously into one of these sites. The second site was left untouched. After another week both sites were tested intracutaneously with a cottonseed extract containing 0.0001 mg. nitrogen per cubic centimeter. This concentration was determined by previous titration to be one which would produce wheals of moderate size. A similar amount of cottonseed extract was injected into a control (nonsensitized) site. After twenty minutes, the reactions were read, and the sizes of the wheals and the erythemas were noted. The comparative sizes of wheals and erythemas on the various sites are recorded in Table XIII. The same experiments were performed on a group of seventeen atopic persons who were not sensitive to cottonseed. The results obtained in this group are also recorded in Table XIII.

TABLE XIII

RESULTS OF TESTS IN WHICH:

1. TWO SITES WERE SENSITIZED WITH COTTONSEED SERUM;
2. AFTER ONE WEEK, ONE SITE WAS PREPARED WITH MOCCASIN SNAKE VENOM;
3. AFTER ONE WEEK, BOTH SITES WERE TESTED WITH COTTONSEED EXTRACT.

	WHEAL LARGER ON		ERYTHEMA LARGER ON	
	SENSITIZED SITES PREPARED WITH MOCCASIN SNAKE VENOM	SENSITIZED SITES NOT PREPARED WITH MOCCASIN SNAKE VENOM	SENSITIZED SITES PREPARED WITH MOCCASIN SNAKE VENOM	SENSITIZED SITES NOT PREPARED WITH MOCCASIN SNAKE VENOM
Nonatopic subjects, 12	41.6%	58.4%	25.0%	75.0%
Atopic subjects, 17	41.2%	58.8%	29.4%	70.6%

When the cutaneous sensitized sites on atopic persons, which had been tested with moccasin snake venom, were retested the following week with cottonseed extract, they responded with wheals which were greater than those on untreated sites in 41.2 per cent of cases. The same procedure on nonatopic subjects produced larger wheals in 41.6 per cent of cases. It is, therefore, apparent from the above figures that atopic and nonatopic skins reacted almost identically in this experiment.

The above results are not unexpected in the light of the findings of Bowman and Walzer. They showed that stimulation of a passively sensitized site impairs its whealing power. This is the result of a "tissue" factor and an "immunologic" factor. The former concerns capillary changes, and the latter applies to reaginic injury. The injection of moccasin snake venom into a passively sensitized site, therefore, impaired its whealing power and diminished its responsiveness to subsequent specific stimulation.

SUMMARY

1. Moccasin snake venom injected into passively sensitized sites tends to impair the whealing power of such sites to subsequent specific stimulation.

2. The erythematous response of such sites is similarly impaired by such treatment.

3. In the above studies on passively sensitized skins, similar results were obtained on atopic and on nonatopic skins.

REFERENCES

1. Peck, Samuel M.: Proc. Soc. Exper. Biol. & Med. **29**: 579, 1932.
2. Peck, Samuel M., and Rosenthal, N.: J. A. M. A. **104**: 1066, 1935.
3. Goldman, Joseph L.: Arch. Otolaryng. **24**: 59, 1936.
4. Peck, S. M., Rosenthal, N., and Erf, L. A.: J. A. M. A. **106**: 1783, 1936.
5. Bowman, K. L.: J. ALLERGY **7**: 39, 1935.
6. Bowman, K. L., and Walzer, M.: J. Immunol. **29**: 8 and 81, 1935.
7. Bowman, K. L., and Walzer, M.: J. ALLERGY **3**: 503, 1932.

TIME REQUIRED FOR THE PRODUCTION OF HAY FEVER BY SPORES OF A NEWLY ENCOUNTERED FUNGUS, JOHNSON GRASS SMUT

E. W. Phillips, M.D.
Phoenix, Ariz.

In a recent publication, I[1] have shown that nearly 70 per cent of a group of allergic persons exposed to the pollen of sugar beet, which they had not previously encountered, exhibited positive skin tests to beet in their third season of exposure and that about one-third of those so reacting showed clinical sensitivity to that pollen. The present study, based upon the records of the same group of private patients, records their behavior when, in successive years, they inhaled the spores of a relatively recent invader, Johnson grass smut.

Of all the weeds that grow in central Arizona, Johnson grass is the most troublesome. This primitive sorghum, propagated both by seed and by a fleshy rootstock, fouls irrigation ditches, crops, and pastures. It is difficult to eradicate and practically impossible to exclude. Johnson grass has been abundant in this region for many years, but the smut which attacks its florets has established itself only recently. In 1933 the smutted heads were few and far between. In 1935 the infestation had become much heavier, and smut spores were numerous on pollen slides.

The sooty black smut was collected and extracted by Coca's method. The colorless extract, rather low in its protein content, was given a thorough test in the allergy clinic; it elicited no positive reactions. Extracts were then made by other methods and tried with the same results. At that time the members of the group of allergic persons under observation, after at least two years of adequate exposure, showed no cutaneous sensitivity to Johnson grass smut.

Nevertheless, because of its abundance in the air throughout the greater part of the year (Johnson grass grows and pollinates from April to frost in December), it seemed desirable to establish the botanical identity of this smut. This proved to be a difficult undertaking. The plant pathologists consulted, including those at the University of Arizona, were acquainted with the fungus, but had not classified it. It was not until 1939 that my sporadic efforts at identification were successful, and then only as to genus; authorities differ as to species. Streets,[2] of the University of Arizona, says: "This smut is *Sphacelotheca sorghi* and is the same fungus which causes covered kernel smut of grain sorghums. The fungus has become very much more common on Johnson grass than on the grain sorghums as the varieties grown in Arizona are not very susceptible to this smut.

"We have been watching the smut on Johnson grass with interest since we first observed it some eight years ago, and we note a constant spread and considerable increase in prevalence each year. This would be of importance in connection with your finding that it is a cause of allergic rhinitis."

Stakman,[4] to whom Dr. Wittich[3] kindly submitted a specimen, reported as follows: "The smut on the Johnson grass is either *Sphacelotheca cruenta* which also attacks sorghum, or is a new species or race to be designated as *S. holci*. There is still some doubt about its taxonomic position as several taxonomists are still working on it."

Whatever its specific name, there is no doubt about the prevalence of the spores of this parasite in the Phoenix district. It appears on slides in April, and on Dec. 3, 1939, a supply for laboratory use was easily collected.

The failure to elicit any positive skin reactions with this smut was puzzling, and each year I repeated the test on patients whose history was suggestive or whose result from adequate pollen therapy was for some unexplained reason incompletely successful. Not until the fall of 1938 were any positive reactions observed; after that they occurred with increasing frequency. In 1939 I was particularly interested in determining the presence of *Coccidioides immitis* in this region. The question of crossed or group reactions to fungus derivatives came up, and Johnson grass smut was used in routine testing. The work on *Coccidioides* and its etiological relation to certain cases of asthma will be reported later. In this investigation, Johnson grass smut was not found to interreact with coccidioidin, nor with other mycotic derivatives, nor with Johnson grass pollen. Its reaction apparently was specific.

In 1939, 131 allergic persons were tested intradermally with about 0.02 c.c. of a 1:500 extract of Johnson grass smut. Thirty-four, or about 26 per cent, had typical positive reactions, with pseudopods, flare, and a wheal 1 cm. or more in diameter. Without exception, these positive reactors had resided in the Phoenix district for at least five years; several had shown no reaction to smut tests in earlier seasons.

In none of these positively reacting cases was smut the primary cause of hay fever; other inhalants, usually pollens, had been the first offenders. The mischief done by the smut consisted essentially in the production of recurrences of hay fever or asthma in patients who were protected by otherwise adequate treatment. The accuracy of this hypothesis was shown by the prompt relief which occurred when smut extract was administered. This sequence of unexpected upset, relieved by smut therapy, was seen in fifteen cases. The other patients reacting to smut received it in addition to their regular pollen therapy and, with one exception, had no relapse. One patient had a mild constitutional reaction from her test dose of smut extract. The effect of intensive exposure

was seen in the case of a small boy who, while impersonating one of his movie heroes, "made a moustache" by daubing the smut on his upper lip. His nasal occlusion and asthma lasted for several days.

COMMENT

From the slowness with which it produces sensitivity, and particularly in view of the fact that the spores are in the air for at least eight months of the year, it seems proper to conclude that the atopen of Johnson grass smut is relatively weak as compared to that of sugar beet pollen and, by inference, of other common pollens. This observation coincides with that of Wittich,[5] although in his studies, the grain smuts, present in greater quantity and over a longer period of time, were more important clinically than has so far been indicated in the present discussion. It is quite possible that the effect of *Sphacelotheca* smuts in Arizona may continue to increase. Wittich reports the nitrogen content by weight of his grain smuts to be about 3 per cent, as contrasted with about 5 per cent in the hay fever pollens. The nitrogen content of Johnson grass smut, in one analysis by the Kjeldahl method, was 2.75 per cent.

The observation that Johnson grass smut is constantly spreading may have an economic significance, apart from its effect upon the health of the population. Stock raising is an important industry in Arizona; Johnson grass invades practically all irrigated pastures, and cattle eat the smutted heads. The belief that smutted grass causes sickness among cattle is common, although proof is lacking. This grass, under certain unfavorable conditions, is known to produce hydrocyanic acid in quantity sufficient to kill animals that eat it. Infestation by smut, however, has not been shown to induce such toxicity.

SUMMARY

Johnson grass smut, variously classified as *Sphacelotheca sorghi*, *S. cruenta*, or *S. holci*, was first observed in Arizona in 1931, and by the writer in 1933. Its distribution and prevalence have increased each year. Spores of this smut are found by gravity on slides during eight or more months of each year, and they are at times by far the most numerous particulate objects so found.

Extracts of this smut, used intradermally in testing hay fever patients resident in Arizona, elicited no positive reactions in 1935, and none in subsequent years until the fall of 1938.

In 1939, 131 persons known to be sensitive to inhaled allergens were tested with smut. Thirty-four had clear and typical positive reactions; one had a mild shock from the intradermal test. All the positive reactors had lived for at least five years in regions where the smut was prevalent.

Fifteen of the positive reactors experienced recurrences of hay fever or asthma and were promptly relieved when smut extract was added to

their otherwise adequate treatment. So far, the smut has been a subsidiary, rather than a primary, cause of inhalant allergy.

In this series of cases, at least five seasons of exposure to the spores of Johnson grass smut were required to induce cutaneous and clinical sensitivity to that fungus.

REFERENCES

1. Phillips, E. W.: Time Required for the Production of Hay Fever by a Newly Encountered Pollen, Sugar Beet, J. ALLERGY **11**: 28, 1939.
2. Streets, R. B.: Personal communication.
3. Wittich, F. W.: Personal communication.
4. Stakman, E. C.: Quoted by Wittich.[3]
5. Wittich, F. W.: Further Observations on Allergy to Smuts, Journal-Lancet **59**: 382, 1939.

ERYTHEMA NODOSUM FROM SULFANILAMIDE

Some Experimental Aspects

Adolph B. Loveman, M.D., and Frank Simon, M.D.
Louisville, Ky.

TEDDER[1] has recently reviewed the literature on the cutaneous reactions from sulfanilamide. Since the appearance of this paper, an example of fixed eruption with stomatitis[2] and cases of bullous eruptions[3, 4] following sulfanilamide therapy have been reported. It is felt that a further review at this time would be superfluous. Although diverse reactions are constantly being observed and reported, we have been unable to find, in a rather careful search of the literature, any case of erythema nodosum from sulfanilamide. This unique feature, in addition to the fact that our patient permitted extensive investigative work, warrants, in our opinion, a brief case report.

CASE REPORT

History.—I. M. S., female, aged 23 years, entered the Susan Speed Davis Home on Feb. 8, 1939, to complete arrangements for the care of her 3-week-old baby. The rest of the history was unimportant, but included a denial of any allergic history or previous skin eruptions. The physical examination was essentially negative, with the exception of a vaginal and urethral discharge from which gonococci were demonstrated. All other laboratory data were essentially negative, including a Kahn test on the blood.

Course in the Hospital.—Beginning February 17, the patient was given the following amounts of sulfanilamide: 1.3 Gm. four times daily for two days; 0.97 Gm. four times daily for five days; 0.65 Gm. four times daily for seven days; 0.32 Gm. four times daily for fourteen days.

On March 13, the patient noticed swollen tender areas on the lower right leg. She was given magnesium sulfate packs, with elevation of the affected limb.

On March 16 she was sent to the City Hospital and was seen in the Department of Dermatology and Syphilology. The physical examination, other than the cutaneous findings and a temperature of 102.4° F., was essentially negative. She presented an eruption confined, for the most part, to the knees and lower legs. This consisted of bean- to quarter-palm-sized, excruciatingly tender, erythematous nodules. The skin overlying these nodules was tense and shiny. There were a few scattered pea-sized erythematous macules over the shoulders. The mucous membranes were unaffected.

A diagnosis of erythema nodosum was made and experimental investigations were begun.

Diagnostic Possibilities.—Clinically, this patient had typical erythema nodosum, but it remained to be determined whether this was a classic erythema nodosum of undetermined origin (tuberculous or strepto-

From the Departments of Dermatology and Syphilology and Medicine of the School of Medicine, University of Louisville, Louisville, Ky.

coccic?) caused from her gonorrheal infection, or an allergic response from sulfanilamide. It is interesting to note here that sulfanilamide has been used in the treatment of certain cases of erythema nodosum with gratifying results. The facts that there was no evidence of tuberculosis and that the patient had been taking large doses of sulfanilamide made it rather unlikely that we were dealing with a streptococcic, tuberculous, or gonorrheal erythema nodosum.

In addition to the above perhaps we should at least mention biotropism, or the synergistic action of the drug plus some other infectious agent, as a possible etiological mechanism. (Dr. Sulzberger first called this to our attention.) Against such a theory, however, is the threefold repetition of the production of lesions. Furthermore, this patient, according to her history, had never before had erythema nodosum from any cause, and she did not have an attack during her neisserian infection prior to the taking of sulfanilamide. The initial attack was preceded by the usual incubation period commonly found in cases of dermatitis medicamentosa, which period was markedly shortened in the two subsequent attacks. From the above, therefore, although we cannot rule out completely the theory of biotropism, it is certainly only a very remote and rather unlikely possibility.

Reproducing the Eruption.—Immediately upon seeing this patient, it was suggested that sulfanilamide be discontinued. Four days later she was reexamined. The temperature was now normal, and, other than slight pigmentation upon the sites of the previously involved areas, all of the eruption had disappeared.

On March 19, she was again started on sulfanilamide and was given a total of 240 grains (16 Gm.) over a period of two and one-half days. About eighteen hours after commencing the drug, she noted pain and swelling about the left knee, but she continued with the medication.

On March 21, she was again examined in the clinic. The lesions had returned and were similar in every respect to those for which she was previously examined. The temperature at this time was 100.4° F. A blood count revealed no significant deviation from the normal, with the exception of a slightly reduced red blood count (3,720,000).

Although we were reasonably certain as to the cause of the eruption, it was clinched by reproducing it again. There has been no recurrence since the drug was discontinued some ten months ago. The patient was last examined Dec. 20, 1939.

Cutaneous Tests.—The following tests were performed on the patient in both normal and previously involved skin areas, and on a nonsensitive control.

1. Sulfanilamide, saturated aqueous solution, 0.10 c.c. intradermally.

2. The patient's blood serum taken at the height of the eruption (caused by sulfanilamide taken by mouth), 0.10 c.c. intradermally.

3. An extract of a piece of the patient's skin removed from a lesion and made by emulsifying the tissue in Coca's buffered saline solution and filtering through a sterile Berkefeld filter, 0.10 c.c. intradermally.

4. Same as Test 1, except that the solution was applied by patch test.

5. Same as Test 2, except that the serum was applied by patch test.

6. Same as Test 3, except that the extract was applied by patch test.

Readings were made immediately (fifteen to thirty minutes) in the case of the intradermal tests, and, also, two days later in all tests, both intradermal and patch. All tests were negative.

Biopsy.—On March 22, a biopsy was taken from a typical nodule and submitted to the department of pathology for study. The report of Dr. Harold Gordon of this department is quoted in full: "The material consists of a small piece of skin and subcutaneous tissue. The epithelium shows no essential pathologic changes. There are a few small focal areas of recent inflammation in the superficial portion of the corium, about some of the rete pegs. These foci are rich in lymphocytes and monocytes and have small but prominent new-formed vessels. The most marked changes are present in the deeper portions of the corium and in the subcutaneous adipose tissues. Here there are numerous inflammatory foci about small vessels. These foci are rich in polymorphonuclears, many of which show chromatolysis. In addition, there are many eosinophiles and monocytes, a lesser number of lymphocytes. Many of the foci show early caseation necrosis. The vascular changes also are prominent. Some of the vessels are thrombosed; all are prominent and most have large, pale, swollen endothelial cells in the intima. Some of the older lesions are less cellular than those described above and are characterized by the presence of multinucleated giant cells with a vacuolated cytoplasm. The giant cell reaction is discrete and lies at a distance from the acute focal lesions previously described. Diagnosis: Erythema nodosum."

Dr. Hamilton Montgomery of the Mayo Clinic concurred in the above opinion. In addition, he stated: "In one area, both within the foreign body giant cell and adjacent thereto in other cells, several organisms suggestive of bacilli and possibly of diphtheroids were to be seen with hematoxylin and eosin stain. Further sections and further stains are indicated to determine the signicance of the presence of these bacilli. There is nothing in the histologic picture to suggest a dermatitis medicamentosa and if bacilli are demonstrated in further sections this would speak for an ordinary type of erythema nodosum and against the reaction being one due to sulfanilamide."

Following his suggestion, further sections were made and reported by Dr. Gordon as follows: "Special stains (Gram's method and methyiene blue) reveal a few intracellular gram-negative diphtheroids and a very occasional gram-positive rod. These are present only in the monocytes and epithelioid giant cells of the older lesions. I interpret the giant cell reaction and the acute inflammatory changes as not necessarily directly related. Probably the giant cell reaction is part of an older lesion, possibly a residual change due to previous inflammatory stimuli, since the giant cell reaction is separate and distinct from the necrotizing inflammatory changes. This interpretation seems to be strengthened by the fact that the giant cells are of typical foreign-body type containing many cytoplasmic vacuoles. It is not unlikely that these vacuoles represent the remains of ingested damaged fat cells. The fact that organisms are found only in the giant cells and not in or about the recent necrotizing lesions suggests the acute lesion now present is essentially of nonbacterial etiology and indicative rather of a recent hematogenous reaction to the sulfanilamide injections."

It may be inferred by those who do not share Dr. Gordon's explanation that the finding of bacilli lends additional support to the theory of biotropism. We feel, however, that, although these observations are interesting, they should not be considered pathognomonic of bacterial erythema nodosum, because the finding of bacilli is not a universal one, even in cases in which the etiology is known to be an infectious agent.

We believe, furthermore, in view of the practically foolproof evidence in support of drug origin in our case, that the importance of such findings in the past may be minimized.

DISCUSSION

This case affords an excellent illustration of what we have continually emphasized, namely, mimicry by drugs of conditions often unrelated to drugs. Not only can drugs simulate practically any cutaneous entity, but likewise they can mimic numerous nondermatologic conditions. Such things as jaundice, agranulocytosis, purpura, headache, nausea, paresthesias, pains in the brachial plexus, toothache, and many other complaints have resulted from drug therapy. If such facts are so universally established, it is not inconceivable that the future will reveal many other vague and obscure visceral symptoms to be of drug origin.

The histologic section also emphasizes the accuracy of drug mimicry. There is nothing in the section to suggest drug origin, even after careful study. Such a biopsy further stresses the importance of correlation of the clinical and histologic findings before arriving at an accurate diagnosis. It is not fair to expect too much of the pathologist. He can only describe what he sees, and the responsibility of interpretation usually rests with the physician who submits the tissue for study.

Unfortunately, many physicians still cling to the belief that erythema nodosum is of either streptococcic or tuberculous origin. We do not share such an opinion, but feel rather that this condition may be the result of multiple etiologies. Typical cases of erythema nodosum with all of the classic signs and symptoms have resulted from diverse infectious agents as well as from drugs. Wise and Sulzberger[5] have emphasized repeatedly this viewpoint in recent years, although Stelwagon[6] and Osler[7] years before mentioned such a possibility.

Judging from personal experience as well as from reports in the literature, erythema nodosum resulting from drug ingestion is rare. The most frequently offending drugs are iodides, and bromides, although antipyrine, arsenic, and phenacetin are sometimes responsible. There is no reason for us to believe that the particular case under consideration is in any way unique except with regard to the particular drug which caused the syndrome. There was unquestionably much evidence pointing to other causes of the erythema nodosum, and it was only after carefully appraising this evidence and reproducing the condition that the definite etiology was established. In many cases of erythema nodosum, there is a history of recent drug ingestion. In such cases it is suggested that the particular medication be stopped and that the course of the disease be observed. When all signs of the symptoms have disappeared, the judicious readministration of the drug is indicated in an attempt to reproduce the condition. In this manner, more cases of erythema nodosum will undoubtedly prove to be of drug origin.

Wise and Sulzberger[8] have emphasized the fact that biologic reactions are much more sensitive than are chemical tests. In known cases of phenolphthalein eruptions, chemical tests for the detection of the drug were negative in both urine and involved tissue. These authors likewise were unable to detect the drug by cataphoresis in proved cases of dermatitis medicamentosa from phenolphthalein. We have likewise been unable to detect the drug in suspected cases, and this has caused us to speculate as to the reason for our failure to do so. Is it because of a lack of sensitivity of the chemical test, or is it possible that the eruption is not due to the drug per se? Perhaps some split product of the drug or some unknown allergenic substance is responsible.

In an attempt to answer some of these questions, we planned a series of tests preferably to be performed in a case of fixed eruption. Unfortunately, we were not able to secure a suitable subject for carrying out the work as originally planned. We did, however, have the opportunity of performing certain of the cutaneous tests. Despite the fact that these were entirely negative, it is felt that the results were worth reporting. Such tests should be repeated in the future in cases of fixed eruptions, along with other investigations akin to those suggested above.

Since it is usually impossible to detect the drug chemically in the local tissue, we conceived the idea of making a local tissue extract from such cases and feeding this by mouth to either the particular patient or to some other equally hypersensitive person. If we could thus reproduce the eruption in the absence of demonstrating the drug chemically in the tissue, we would have additional proof not only of the fact that biologic reactions are more sensitive than chemical tests, but also that either the drug or some split product of the drug was present in the tissue.

As a rule, both intradermal and patch tests are negative in cases of dermatitis medicamentosa. The most logical explanation of this is that of Wise and Sulzberger, namely, that the seat of sensitivity or shock site is deep in cases of noneczematous drug eruptions, and hence one would not expect to find positive patch tests. It may be, however, that we are not testing with the right material. In other words, perhaps some chemical change has taken place in the drug after it is ingested and this newly formed chemical is responsible for the eruption rather than the drug per se. Therefore, in addition to feeding the extract by mouth, we also proposed to perform patch and intradermal tests with the patient's blood serum taken at the height of concentration of the drug, as well as with an extract made from the local involved tissue. The significance of such tests, had they been positive, would have been obvious, especially in view of the usual negative cutaneous tests and the failure to demonstrate the drug in situ.

CONCLUSIONS

A case of erythema nodosum from sulfanilamide is reported.

The histopathology was indistinguishable from the classic type of erythema nodosum.

Chemical tests of tissue taken from an active nodule were negative for sulfanilamide.

Patch and intradermal tests with a saturated solution of sulfanilamide on both normal and previously involved areas were negative.

Patch and intradermal tests with a tissue extract taken from an active nodule and with the blood serum taken at the time of the highest blood sulfanilamide concentration were negative on both normal and previously sensitized areas.

REFERENCES

1. Tedder, J. W.: Toxic Manifestations in the Skin Following Sulfanilamide Therapy, Arch. Dermat. & Syph. **39**: 217, 1939.
2. Loveman, A. B., and Simon, F. A.: Fixed Eruption and Stomatitis Due to Sulfanilamide, Arch. Dermat. & Syph. **40**: 29, 1939.
3. Bettley, F. R., and Simon, P.: A Bullous Eruption Due to Sulfanilamide, Brit. M. J. **1**: 1177, 1939.
4. Epstein, Ervin: Bullous Eruption Following Sulfanilamide Therapy, Arch. Dermat. & Syph. **41**: 1, 1940.
5. Wise, F., and Sulzberger, M. B.: Year Book of Dermatology and Syphilology, 1931, p. 84; 1932, p. 82; 1933, pp. 111, 114; 1937, pp. 145, 483, 484; 1939, p. 163.
6. Stelwagon, H. W.: A Treatise on Diseases of the Skin, ed. 9, Philadelphia, 1921, W. B. Saunders Co., p. 151.
7. Osler, W.: The Principles and Practice of Medicine, ed. 10, New York, 1926, D. Appleton & Co., p. 366.
8. Wise, F., and Sulzberger, M. B.: Drug Eruptions: Fixed Phenolphthalein Eruptions, Arch. Dermat. & Syph. **27**: 549, 1933.

FOOD SENSITIVITY AS A FACTOR IN THE ETIOLOGY OF ACNE VULGARIS

FRANK E. CORMIA, M.D.
MONTREAL, QUEBEC

THERE have been but few statements concerning the relationship between the ingestion of certain foods and the development and persistence of acne vulgaris. The present paper is a study of the food factor in relation to the disease.

LITERATURE

Carbohydrates have been incriminated as a causal agent in acne for many years. Despite normal blood sugar and normal sugar tolerance values in the great majority of patients, the low carbohydrate diet in acne has enjoyed a popularity exceeded perhaps by no other form of diet in any cutaneous disease. The work of Crawford and Swartz[1] is especially interesting in this regard. Ten patients were found to have normal blood sugar values and were then hospitalized and placed on a controlled high carbohydrate diet with a daily addition of intravenous dextrose. Seventy per cent of these patients were improved, and none were made worse. I believe that a low carbohydrate diet is beneficial only when secondary invasion by staphylococci has occurred.

There are few references in the literature concerning the relationship of specific foods in the production of acne vulgaris. Buckley[2] noted that bananas and nuts frequently aggravated acneform eruptions. Wells[3] considered diet to be a factor in the causation of acne and incriminated cheese, eggs, pork, and chocolate. Specific effects were noted after the ingestion of pork in 25 per cent of his patients, often appearing within twenty-four hours after ingestion, and were likely to persist for several days. Rowe[4] described a case in which elimination diets effected a complete cure of a long-standing acneform eruption. He later reported similar cases treated by the elimination of certain foods.[5] White has studied a number of cases of acne vulgaris from the standpoint of food sensitivity, and he believes that foods play an important role in the resistance of many cases to routine local and x-ray therapy. He first noted the case of a woman with acne of seventeen years' duration,[6] for which much therapy, including x-rays to the point of telangiectasia and atrophy, had been given. She was greatly improved by the elimination of eggs and wheat from the diet. He later reported a series of thirty-two similar cases,[7] all of whom had a papulopustular acne in the usual distribution. He noted that seborrhea, formation of comedones, and

seborrhea of the scalp were absent or were present in minimal degree. The lesions were more commonly papular than pustular in nature. White believed that this absence of seborrhea and the presence of only a minimal element of pustulation was very suggestive of food sensitivity. However, the point should be emphasized that all these patients had received a considerable amount of x-ray therapy, sufficient in most instances to control the elements of seborrhea and pustulation. White found that chocolate, milk, wheat, oranges, tomatoes, and nuts were the foods most frequently incriminated. Especially adapted elimination diets were of more value than skin testing in the detection of sensitivity. Each patient was put on a nonallergic type of diet for one week, after which suspected foods were added at two-day intervals. Reactions occurred after from two to twenty-four hours.

Cunningham and Mendenhall[8] performed scratch tests in forty-two patients with acne. They found that spinach, pork, and potatoes frequently gave positive reactions, and stated that about 75 per cent of their group of patients were from 50 to 100 per cent improved by food eliminations. In their opinion, all patients with acne were sensitive to food proteins, but they stated the belief that other factors, such as endocrine disturbances, could produce acne in a small group of the patients. If a food was ingested by a patient specifically sensitive to that food, a papule appeared first. If ingestion was continued, large pustular lesions occurred. The development of pustular lesions noted by Cunningham and Mendenhall is in contradistinction to the belief of White, in whose experience the lesions were largely papular. It is noteworthy, however, that none of the patients of Cunningham and Mendenhall had been given roentgen-ray therapy. In the discussion of this paper, Sulzberger stated that he considered foods to be an insignificant factor in the production of the bulk of cases of acne vulgaris. In his opinion, the acne probably occurred on the basis of a hyperstimulation by, or a sensitivity to, hormones. Wise and Sulzberger,[9] in commenting on the improvement noted after a reduction of sweets and starches, stated the belief that the ill effects noted after high carbohydrate diets were in some instances due to an idiosynerasy to certain specific items in the high carbohydrate diet. They mentioned particularly chocolate and white bread. The aggravations which occurred after the ingestion of white bread were not considered to be evidence of specific food sensitivity, but were believed to be caused by improvers in the bread. These improvers contain potassium bromate which, in the process of baking, becomes reduced to bromine. Because of their high iodine content, certain foods, including spinach, sea foods, cabbage, lettuce, and artichokes, were to be prohibited. There is no doubt that the excretion of iodine and bromine through the pilosebaceous apparatus will aggravate an existing acne or it may, not infrequently, be the sole agent in its production.[10]

MATERIALS AND METHODS OF THE PRESENT STUDY

In a series of eighty private patients with acne vulgaris, an element of food sensitivity was suspected in twenty-five. In twenty of this group, elimination diets were given. Twelve additional patients, all with severe acne of two or more years' duration, but lacking a history of food sensitivity and the clinical features commonly noted in patients with acne in which an element of food sensitivity occurred, were included as a basis for comparison. In thirteen of the group of thirty-two patients, skin testing was done with the common food allergens, and the results were compared and checked against the results obtained by the elimination diets.

Of the thirty-two patients, twenty-two were females and ten were males. Their ages varied from 15 to 34 years, with an average of 22. The duration of the disease varied from 2 to 17 years, with an average of 5.7. Twenty-eight patients had received previous treatment; roentgen-ray therapy to an average total of 850 r. units had been given to fifteen patients.

PREDISPOSING CAUSES AND AGGRAVATING FACTORS

The family history in the entire group was of importance because of the frequency of acne and seborrhea (twenty-two) and of infection (seventeen). A definite history of atopy, however, was present in but ten families. The personal history was positive for allergic manifestations in but four instances, and one of these was infantile eczema. Focal infections occurred seventeen times in fifteen of the thirty-two patients. Menstrual irregularities were noted in nine of the twenty-two female patients. An important feature was the known ingestion of iodized salt in twenty-three of the thirty-two patients; five other patients were probably using iodized salt. One of this group had been given iodine for the treatment of the acne, and a severe flare-up of the lesions occurred. A patch test with potassium iodide was positive in this case.

The chief aggravating factors learned from the history were as follows: inadequate hours of rest, twenty-two; aggravation by menstrual periods, fourteen; and aggravation by alcohol, four. Sixteen patients believed that one or more foods had caused a flare-up of the eruption. In only two cases, however, was there any suggestion of an aggravation by an active focus of infection or by an acute upper respiratory infection, and none of the patients were found to be sensitive to light.

GENERAL PLAN OF TREATMENT

All patients were given mild local astringents, and local treatment was given for the care of seborrhea of the scalp, when present. The use of iodized salt and of alcohol was interdicted, and adequate hours of rest were prescribed. All patients were placed on elimination diets, and skin testing was done when possible. Roentgen-ray therapy was used in

most patients for the treatment of residual seborrhea or resistant papulopustular lesions, but was generally delayed until food testing was nearly complete so as to avoid false negative reactions to foods to which only a mild sensitivity was present. A small total dosage scale was used in all instances. Attempts were made to remove all existing foci of infection. Endocrine therapy was likewise given in the few instances in which it seemed indicated.

DETERMINATION OF THE ELEMENT OF FOOD SENSITIVITY

Acne Elimination Diet.—Diet 1.—Milk, 2 or 3 quarts daily for two days. Includes buttermilk, cream, and seltzer water.

Diet 2.—Basic diet, to be continued for four days: lamb; rice, carrots, beets; peaches, pears, lemons. Miscellaneous: olive oil, unstuffed olives, gelatin, maple syrup, sugar, butter, and salt. Salt must be plain, not iodized. Gravies must be thickened with rice flour. Pure rye bread. Milk, if patient is not sensitive.

Diet 3.—This is a changing diet, consisting of four groups of foods, each to be taken for three-day periods. The miscellaneous foods are those listed in Diet 2. Milk may be added, if patient is not sensitive.

1. Chicken, eggs; turnips, corn; apricots, prunes; tea.

2. Beef; cabbage, lettuce, cauliflower; grapefruit, apples, pickles; coffee.

3. Whitefish (fresh-water fish, if possible); potatoes, onions, celery; bananas, pineapple.

4. Pork and bacon (lamb may be substituted); peas, string beans; apples, grapes, oranges.

Diet 4.—To the basic diet, with additions, if necessary, from Diet 3, add successively, one at a time, for two-day periods, the following foods: wheat (if no reaction, add white bread); spinach; nuts; tomatoes; chocolate.

Diets modified initially from Rowe's elimination diets were prepared and then altered so that the most commonly reacting foods would be given near the termination of the diet. When reactions to a group of foods occurred, special diets were devised to meet individual requirements. When positive reactions occurred to any food or group of foods, the lesions were allowed to subside on a nonallergic type of diet before new test foods were added.

CORRELATION OF HISTORY OF INFECTION, ALLERGY, AND TYPE OF ACNE WITH THE ELEMENT OF FOOD SENSITIVITY IN FIFTEEN PATIENTS IN IN WHOM FOOD ELIMINATIONS WERE OF VALUE

It is especially noteworthy that, of fifteen patients in whom food eliminations were of value, there was a family or personal history of infection in twelve. Focal types of infection were present in the families of nine patients, while in seven there was a personal history of such infection. On the other hand, a history of allergy, either familial or personal, could be obtained in but five instances. It is interesting to speculate on a possible relationship between these facts and the element of food sensitivity, and the conclusion is suggested that reactiveness to

foods, whether or not it is a true sensitivity, is not usually accompanied by other forms of allergy. The skins of this group of fifteen patients were commonly thin and delicate; the element of pustulation was variable, but was likely to be moderate in character, and the papular and pustular lesions were frequently surrounded by erythematous flares. The amount of seborrhea ranged from minimal to moderate in most patients, while three had dry, rather than oily, skins. This diminution in the amount of seborrhea, in comparison with that usually seen in cases of acne, did not seem to be of especial significance with regard to the element of food sensitivity, but could be correlated, as a rule, with the amount of previous roentgen-ray therapy and with the use of local drying applications.

CORRELATION OF THE ELEMENT OF FOOD SENSITIVITY WITH A HISTORY OF AGGRAVATION BY FOODS

A history of aggravation by twenty-four different foods was given by sixteen of the thirty-two patients. The foods most frequently mentioned were chocolate (twelve) and tomatoes (three). Other foods incriminated were pork, potatoes, cheese, bread, eggs, apples, tea, coffee, and oranges. Seven of the twelve patients with suspected chocolate sensitivity reacted positively when chocolate was eaten. Four others refused to make the test because of severe previous reactions. Two of the three patients with suspected sensitivity to tomatoes reacted positively, as did four patients who complained, respectively, of aggravation by potatoes, cheese, white bread, and eggs. Of the twenty-four foods, thirteen were found to cause a flare-up of the eruption on ingestion. Considering the four patients not tested because of previous severe reactions, the conclusion may be drawn that a history of aggravation by a specific food or foods usually may be taken as evidence of a food sensitivity.

CORRELATION BETWEEN INGESTION TESTS AND CUTANEOUS REACTIONS TO SCRATCH AND INTRADERMAL TESTS

Comparisons were made between the results of ingestion tests and intradermal reactions in thirteen patients. Scratch and intradermal tests were performed with a large number of foods. Scratch tests almost uniformly gave negative results, but there were many reactions to the intradermal tests. Generally speaking, the patients who reacted most vigorously to the ingestion tests gave positive intradermal reactions to the food in question. However, there was no correlation between the degree of reaction to the ingestion tests and the degree of positiveness of the intradermal reaction. In some instances, patients who had developed from ten to thirty lesions after food tests gave weakly positive intradermal tests, and in two patients the reactions to intradermal tests were negative. In the present series, the rather large number of foods

to which a positive reaction was obtained by intradermal testing were routinely eliminated from the diet. After the improvement of the eruption, these foods were gradually reintroduced into the diet, and only rarely did they cause subsequent reactions. There is a possibility that some of these foods may have caused minor aggravation of the lesions, but this could not be detected by a further study of the patients.

In general, it may be said that there was little or no correlation between the results of skin tests and the clinical role of the respective foods in the production of exacerbations of acne.

SENSITIVITY TO FOODS AS SHOWN BY FOOD TESTING

The foods which most frequently caused demonstrable flare-ups were as follows: chocolate, sixteen (fifteen patients refused the test); tomatoes, eight; nuts, seven; spinach, five; wheat, white bread, coffee, and potato, four; eggs, peas, and grapefruit, three; milk, string beans, tea, two. The following foods caused a flare-up in one instance each: beef, oatmeal, fish, corn, carrot, lettuce, beet, cheese, and cabbage.

Interestingly enough, four patients reacted positively to white bread, but gave negative reactions to wheat. This is confirmatory evidence of the belief of Wise and Sulzberger that bread improvers containing bromates could, at times, be responsible for flare-ups.

Reactions were further studied from the standpoint of their intensity. The average number of lesions which appeared after ingestion of specific foods was as follows: wheat, thirteen; tomatoes, eleven; milk, nine; chocolate, seven; nuts, seven; spinach and white bread, six; string beans and oranges, five; eggs, peas, and grapefruit, four. The number of lesions appearing after ingestion of foods causing a flare-up on a single occasion were: oatmeal, fifteen; beef, ten; fish and corn, eight; oranges, five; and cheese, four.

Considerable difficulty was encountered at times in determining whether or not the flare-ups were due to the ingestion of the suspected food or to other causes. To eliminate the possibility of such errors, all reactions occurring before, during, or immediately after the menstrual period were discounted, and the test was repeated. Flare-ups occurring after the ingestion of alcohol, inadequate hours of rest, or those noticed in conjunction with an acute focus of infection were likewise discounted. Other patients, who showed flare-ups consisting of from four to ten lesions while on a previously nonallergic diet, but in whom an endocrine influence was suspected, were eliminated from the calculations. As a general rule, a reaction of less than five papular or papulopustular lesions was not considered evidence of food sensitivity unless the lesions were unduly large.

When foods caused specific aggravation of the eruption, this usually occurred within twenty-four hours, and, in patients in whom marked

sensitivity was present, the reaction was sometimes seen after two hours. Lesions generally appeared, however, between twelve and twenty-four hours after the suspected food was first eaten. In some instances, and this seemed to be particularly true in patients who had received much previous treatment, the lesions developed very slowly after from forty-eight to seventy-two hours.

White noted that milk was a common source of food sensitivity. Only two patients in the present series reacted specifically to ingestion tests with milk, although these two gave strongly positive clinical reactions, developing eight and ten lesions, respectively, within twenty-four hours. Curiously enough, in all of the remaining thirty patients, there was decided improvement when they were placed on a strictly milk diet. On this regime, lesions grew smaller, and the erythematous flares and other evidences of irritability largely disappeared. No reasonable explanation could be found for this fact, except that during this time other foods causing specific reactions were eliminated. It is noteworthy, however, that the same improvement occurred on a strictly milk diet in several patients in whom no evidence of food sensitivity could be determined.

THE RESULTS OF TREATMENT IN TWENTY-TWO PATIENTS WITH POSITIVE REACTIONS TO ELIMINATION DIETS

The results of the treatment with food eliminations, excluding improvement which was the result of other forms of therapy used, were curative in two patients, and showed 75 to 90 per cent improvement in five patients and 50 to 75 per cent improvement in eight patients. The duration of observation after final improvement was adjudged was one year in three cases and from one to three years in the remaining twelve cases. There were seven patients who had clinical exacerbations on the ingestion of one or more foods, but who subsequently relapsed at the completion of the treatment. These patients were further studied in an effort to determine the cause of the relapse. The element of clinical food sensitivity was usually present in only a mild degree. The relapse in none of these patients was complete, being less than 60 per cent in four patients, 75 per cent in two, and 90 per cent in one. A cause for the relapse could not be found in two patients. Three other patients had definite foci of infection. This occurred in two as a resistant sinusitis, and it was not amenable to further therapy. In the third patient, the focus was removed, and a complete recovery ensued. Two patients did not stay on the diet. In one of these, a 40 per cent improvement occurred after the special diet was re-established, but a complete cure was not obtained until two courses of endocrine therapy with theelin and anterior pituitary-like substance were given. The remaining patient, who was extremely resistant to all previous forms of therapy, eventually secured a 90 per cent improvement by the use of the orally active estrogenic substance, stilboestrol.

SUMMARY AND CONCLUSIONS

Certain foods frequently make worse a type of acne characterized by delicate, rather than coarse, skin, by a variable but usually moderate degree of seborrhea, frequently by the presence of erythematous flares around pustular lesions, and by a history of resistance to previous treatment. The use of elimination diets and the subsequent removal of all reactive foods from the diet will result in clinical improvement in from 50 to 70 per cent of the cases in which food sensitivity is suspected. Standard methods of therapy are to be recommended to combat collateral factors and to secure a complete cure.

Approximately 20 per cent of the patients with acne in the practice of the author showed clinical evidence of food sensitivity; 70 per cent of this group were greatly improved or cured by food eliminations.

The foods most commonly found by ingestion tests to cause clinical flare-ups were, in order of frequency, chocolate, tomatoes, nuts, spinach, and wheat.

The foods provoking the largest number of lesions were, in order, wheat, tomatoes, milk, chocolate, nuts, and spinach.

The results of scratch and intracutaneous tests with foods were of little or no aid in the discovery of woods which caused clinical exacerbations.

The incidence of allergy and of other allergic diseases was no higher in this group of acne patients than in any control group of normal persons.

REFERENCES

1. Crawford, G., and Swartz, J.: Acne and the Carbohydrates, Arch. Dermat. & Syph. **33**: 1035, 1936.
2. Buckley, L. D.: Skin Diseases and Internal Disorders, New York, 1906, Rebman Co.
3. Wells, W.: Diet as a Factor in the Etiology of Acne Vulgaris, Practitioner **128**: 331, 1932.
4. Rowe, A. H.: Food Allergy, Philadelphia, 1931, Lea & Febiger, p. 113.
5. Rowe, A. H.: J. ALLERGY **7**: 381, 1936.
6. White, C.: Food Sensitization Dermatoses. Essential Consideration of the Primary Types of Acneform Distribution, J. ALLERGY **4**: 151, 1933.
7. White, C.: Acneform Eruptions of the Face. Etiologic Importance of Specific Foods, J. A. M. A. **103**: 1277, 1934.
8. Cunningham, T., and Mendenhall, J., Observations on Acne and Allergy, J. ALLERGY **7**: 378, 1936.
9. Wise, F., and Sulzberger, M. B.: The Role of the General Practitioner in the Modern Treatment of Acne Vulgaris, The Yearbook of Dermatology and Syphilology, Chicago, 1933, The Yearbook Publishers, p. 10.
10. Sulzberger, M. B., Rostenberg, A., Jr., and Sher, J. J.: Acneform Eruptions: With Remarks on Acne Vulgaris and Its Pathogenesis, New York State J. Med. **34**: 899, 1934.

ALLERGIC RHINITIS AND ASTHMA DUE TO SENSITIZATION TO THE MEXICAN BEAN WEEVIL (ZABROTES SUBFASCIATUS BOH.)

F. W. Wittich, M.D.
Minneapolis, Minn.

THE first cases of allergic rhinitis and asthma due to a species of weevil (*Zabrotes subfasciatus* Boh.) are here reported. The following are the significant clinical, immunologic, and entomologic observations.

CASE REPORTS

Case 1.—A female, aged 36 years, working as a sorter in a seed house for over three years, was seen on Oct. 17, 1938. She complained that during the latter part of the previous and present fall seasons, when sorting peas and beans which were badly infested with weevils, her eyes would burn and itch. She had lacrimation and showed definite irritation of sneezing, blocked nasal passages, and a watery discharge. If she persisted in working, these symptoms were accompanied by attacks of wheezing which would continue until she had quit her work for a few days.

At different seasons, she sorted the stored beans, peas, and corn seeds as they came down a chute. She picked the "buggy" peas and beans from the normal seeds. Corn which she sorted was infested with the Indian-meal moth (*Plodia interpunctella* Hbn.). For the most part she sorted stored peas and beans. The season for the sorting depended upon the growth, early or late, or the time and size of the orders. This was usually from September or October until April or May. During this rush season the number of girls employed was limited, and she would work continuously for days on peas and beans. A week before her first examination she also had an attack of hives, and her eyelids and cheeks became "puffy and swollen." Her mother had seasonal hay fever, chronic eczema, and attacks of angioneurotic edema. The positive physical findings were a definite, pale, glistening, edematous nasal turbinate and a thin watery discharge. There was some edema of the eyelids. There were numerous sibilant râles over both lungs. All symptoms were greatly relieved by administration of 0.4 c.c. of 1:1,000 epinephrine solution.

Numerous skin tests done at a later date with tree, grass, and weed pollens were negative. There were a few mild food reactions, as well as a moderate response to her own seed mill dust. There was no reaction to the hairs, feathers, common air molds, or grain smuts. Carefully selected (hand lens) peas, beans, and corn of the varieties which she was accustomed to sorting and which showed no evidence of being infested, as well as the infested seeds, were extracted separately for forty-eight hours with Coca's solution and passed through a Seitz filter. Pure cultures of the Mexican bean weevil, *Zabrotes subfasciatus* Boh., and Indian-meal moth, *Plodia interpunctella* Hbn., were also extracted in the same manner. Intradermal tests with the extracts of the beans, peas, and corn were negative, but there was a moderate reaction to the extracts of the "buggy" peas and beans. There was no reaction to the corn which was infested with the Indian-meal moth.

Extracts of the moths were made as well as those of the weevils. The weevils were defatted with chloroform and carbon tetrachloride. Extraction was carried out with Coca's buffered saline solution. The total nitrogen was 1.6 mg. per cubic

centimeter. Dilutions of 0.001 mg. nitrogen per cubic centimeter were used for intradermal testing in this case and also in the following one. Opthalmic and nasal tests were done with 0.01 and 0.1 dilutions.

An intradermal injection of 0.03 c.c. of the weevil extract gave a marked wheal with pseudopods 20 to 25 mm. across with a surrounding zone of erythema of about 60 mm. An intradermal test with the moth extract was negative. The same test on two normal persons at the same time was negative.

Normal skin sites were injected with the patient's serum and tested forty-eight hours later with the weevil, moth, pea, bean, and corn extracts. A definite positive reaction to the weevil extract alone resulted.

At a later date a drop of 0.01 dilution of the weevil extract into the conjunctival sac produced a marked redness and itching of the conjunctiva with lachrimation. A small amount of powdered whole weevil after defatting was placed on the end of a tooth pick and blown into the nostrils with a resultant typical allergic nasal response. Hyposensitization treatments were started in February, 1939, with 0.1 c.c. of the weevil extract containing 0.0000001 mg. nitrogen per cubic centimeter. This represented the highest dilution giving the first negative skin response. In six months, the dosage had been carried up to 0.8 c.c. of a 0.01 extract, and the patient started sorting peas and beans which were infested with weevils without recurrence of any symptoms. A perennial course of treatment is now being carried out.

CASE 2.—A female, aged 43 years, was working as a seed sorter in the same plant for the sixth season. She sorted peas, beans, and corn, but had worked almost entirely at sorting peas during the past season. She was first seen Dec. 9, 1938, and complained that on the preceding Thursday, after working in the forenoon with peas of certain varieties which were badly infested with weevils, she developed redness of the conjunctiva with burning, itching, and lacrimation. There were edema of the eyelids, nasal blocking, and a profuse watery discharge. These became worse on the following day, and she noticed marked wheezing and some coughing with no expectoration.

The physical examination showed typical signs of an acute allergic rhinitis and conjunctival redness with marked edema of the eyelids. The pulmonary signs were those of a moderate asthma. The symptoms cleared up markedly with 0.5 c.c. of 1:1,000 solution of epinephrine administered subcutaneously.

One of the patient's sisters had eczema and bronchial asthma.

The patient was tested routinely with all of the antigens as in Case 1. She showed a marked intradermal response to the bean weevil extract (0.001 mg. nitrogen per cubic centimeter) with an irregular wheal of 18 to 20 mm. and a surrounding erythema of 50 to 55 mm. A passive transfer test using the weevil extract was successful. Nasal packs with a 0.01 dilution produced sneezing, marked paleness, and swelling of the nasal mucous membranes with a watery discharge. A mild systemic reaction with asthmatic symptoms followed which required an injection of epinephrine to control. Three normal persons tested at the same time showed negative skin responses. Skin tests with the legumes, corn, typical foods, animal emanations, and fungi were also negative. There was a two-plus reaction to the Indian-meal moth, but this extract was not included in the treatment set. Treatments were started with the weevil extract and have been continued to date with no return of symptoms. As the result with the weevil extract alone was very satisfactory, the Indian-meal moth was considered of no clinical significance.

ENTOMOLOGIC DATA[1-4]

Bean and pea weevils are old pests which for many years have caused enormous damage to leguminous crops throughout the world.

The commonest weevils found in supplies of beans, peas, cowpeas, or lentils in this country are the pea weevil, the broad-bean weevil and the Mexican bean weevil. They are very small insects ranging from one-eighth to one-fifth of an inch in length and bearing tiny hairlike scales which form markings of black or white. These rub off rather easily and may be inhaled when large quantities of infested peas or beans are handled.

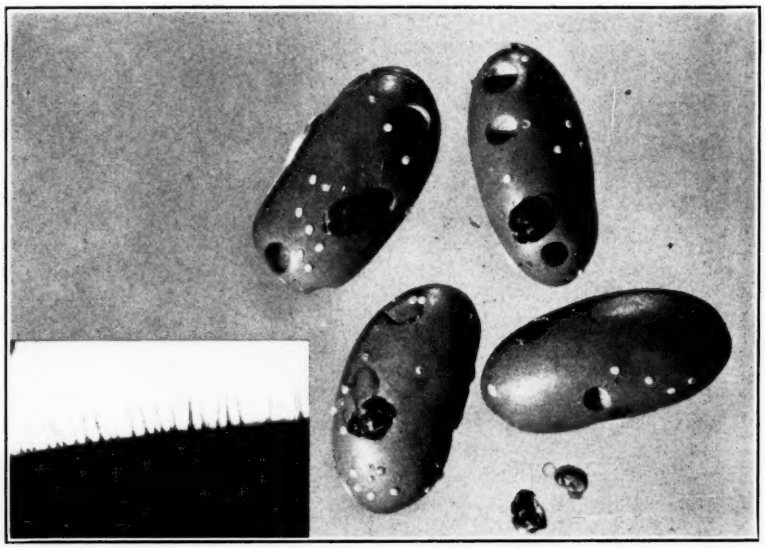

Fig. 1.—Beans infested with the Mexican bean weevil (*Zabrotes subfasciatus* Boh.) which were obtained from the seed mill reported. Insert shows photomicrograph of weevil wing fragment with hairlike scales (magnified about 500 diameters).

The Mexican bean weevil is not generally established in the United States although it is frequently present in peas and beans from Texas and possibly other southern states. According to Shepard,[3] this species was present in 1932 at the seed plant where these patients worked "in such numbers that they may very well have been present there continuously to date." The adult female weevil (about 2 mm. in length) lays its whitish eggs attached to the surface of the dry peas or beans in storage. From these eggs there hatch tiny white grubs that burrow their way into the seeds. When well grown they eat a cavity in the seed up to, but not puncturing, the skin. The grubs then change into the pupae and later into the adults. Each adult has a pair of sharp scissorslike jaws which it uses to cut out a circular flap in the skin of the bean, thus making the small round holes seen in the infested seeds. The insect then crawls out to start another cycle.

These "buggy," or "weevily," peas and beans are very dusty with scales which are inhaled in large quantities. Other girls working in the same plant from fall to spring have shown many of the same symptoms as have the two patients described. One, to my knowledge, was

forced to quit work on account of them. The workers complained that, when the weevils crawled up their arms, they felt an irritation like a slight sticking sensation and small areas of erythema or wheals would form. This was also noted in 1912 by Chittenden[4] of the United States Department of Agriculture. He investigated an illness which broke out among handlers of Italian imported broad beans. They were infested with the broad-bean weevil (*Bruchus rufimanus* Boh.). The men complained that the weevils "crawled up their trousers and bit them, causing nausea, and in addition a rash appeared on the affected parts." The same investigator reported that, in 1909, the Agricultural Department received specimens of two weevils, the four-spotted bean weevil and the common bean weevil from a Texas seed mill, together with the report that, when the infested cowpea seed was being handled, the little insects sometimes covered the bodies of the workers, raising wheals or bumps and actually causing fever.

SUMMARY

Two cases of allergic rhinitis and asthma of entomogenous origin, the first that have been found due to a species of weevil (*Zabrotes subfasciatus* Boh.), are reported.

Symptoms occurred while sorting stored peas and beans, which were infested with weevils, over a long period of time.

An extract of these weevils gave definite skin reactions and passive transfer tests. The patients were satisfactorily treated.

Pertinent entomologic data are presented.

Weevils and moths from the infested peas, beans, and corn from this particular seed mill were identified as belonging to this species by Dr. Harold H. Shepard, Assistant Professor of Entomology and Economic Zoology, University of Minnesota College of Agriculture. Dr. Shepard furnished generous supplies of the weevils and moths for extraction purposes, as well as pertinent entomologic data.

REFERENCES

1. Shepard, Harold H.: Insects Infesting Stored Grain and Seeds, University of Minnesota Agricultural Experiment Station, Bulletin 340, February, 1939.
2. Back, E. A.: Weevils in Beans and Peas, U. S. Department of Agriculture, Farmers' Bulletin No. 1275.
3. Shepard, Harold H.: Personal communication.
4. Chittenden, F. H.: The Broad-Bean Weevil, U. S. Department of Agriculture, Bur. Entomology Bull. 96, Part V, 59-82, 1912.

91 South Seventh Street

RELATIONSHIP OF MOLD REACTIONS TO CLINICAL SYMPTOMS

ROBERT CHOBOT, M.D., HAROLD DUNDY, M.D., AND
NATHAN SCHAFFER, M.D.
NEW YORK, N. Y.

RESPIRATORY allergy due to the inhalation of fungus spores has been receiving increased attention in recent years. Since Van Leeuwen's[1] original observations in 1924 in Holland, there have been many reports in the literature. In America, Cadham,[2] in 1924, was the first to cite a case of asthma due to fungi (wheat rust). Hopkins, Benham, and Kestin[3] reported asthma from *Alternaria* spores, and in another paper, they reported positive cutaneous reactions and positive passive transfer tests in a case of eczema due to *Alternaria*. They also produced an attack of asthma by means of a nasal spray with *Alternaria* extract. Bernton[4] reported a case of asthma due to *Aspergillus fumigatus*. Flood[5] tested fifty-five patients by the scratch method and found eight positive reactors; in one case he succeeded in precipitating an attack of asthma by spraying the throat with a broth filtrate of *Mucor plumbeus*. Jimenez-Diaz and co-workers,[6] in 1932, working with *Mucor*, *Penicillium*, and *Aspergillus*, produced asthma by spraying a pillow with *Penicillium* extract. They found fourteen marked positive reactions in seventeen patients tested, and secured three positive passive transfers. Towey, Sweeney, and Huron[7] reported a group of cases sensitive to maple dust, which, on isolation, was found to be *Conoidosporium corticola*. Their patients had positive scratch tests, negative transfer tests, and did well on environmental removal.

Some work has been done on the incidence of reactions to fungus extracts. Balyeat,[8] in 1932 in Oklahoma, found only 1 per cent of 480 patients tested with positive reactions to the common fungi, and only two clinically sensitive cases. On the other hand, Feinberg,[9] in Chicago, found 28 per cent positive reactions on scratch tests in 243 patients tested. Lamson and Rogers,[10] in 1936 in Los Angeles, tested 1,259 patients, and they found 154, or 12 per cent, reacting to one or more molds by intracutaneous tests. *Alternaria* was found to be the most common offender. No passive transfer tests were performed. Brown[11] noted that, of twenty-four cases tested, there were twelve positive reactions to *Alternaria*. Schonwald,[12] in the Pacific Northwest, tested 150 selected patients with possible mold sensitivity. He found 145 positive reactors, and, of eighty-six cases sufficiently treated, demonstrated defi-

From the Pediatric Allergy Clinic, Department of Pediatrics, New York Post-Graduate Medical School and Hospital, Columbia University.

nite improvement in 76 per cent. Fraenkel,[12] in 1938, found 53 per cent positive reactions to molds in 185 asthmatic patients tested in England, and 15 per cent positive reactors in 522 tested in Germany. He believed the difference in incidence of positive reactions was due to the difference in climate.

There has been little work done concerning the presence of skin-sensitizing antibodies in mold-sensitive patients. Feinberg has stated that in most cases tried, positive passive transfer tests have been obtained, but no mention is made of the number performed.

Feinberg has presented evidence substantiated by scratch tests, mold spore counts, clinical history, and therapeutic trial for the importance of *Alternaria* sensitivity, particularly in seasonal hay fever and asthma. Feinberg used any or all of the following selected group, in whom he suspected mold sensitivity: (1) Patients with a poor response to pollen therapy; (2) patients whose symptoms did not fit in with any known pollen count; (3) patients with an indefinite history of onset or cessation of their pollen symptoms; (4) patients who had negative pollen tests and seasonal symptoms. He found, in his series, positive skin tests by scratch test, and occasional passive transfer tests. Most of his patients had an exacerbation coincident with the increase in spore counts.

The work has been corroborated by Pratt,[14] in Boston, in a large series of atopic children. He, in 1938, reporting on twenty-six *Alternaria* sera tested with undiluted extracts of unknown strength, found twenty-four positive reactors, an incidence of 92 per cent. In the other fungi studied (*Aspergillus, Hormodendron,* and *Penicillium*), there were ten positive reactions in twenty-four sera tested. Atmospheric mold spore counts have been reported by Feinberg, Durham, and Pratt.

These varied reports and the frequency with which we were obtaining positive skin reactions were the reasons for the present investigation. In none of the reports had there been any attempt made to study the serologic response and the neutralization points of the sera. In addition, there were no real indications apparent as to when a patient should or should not be treated. The usual procedure with a pollen-sensitive patient has been to omit mold therapy unless the patient has done poorly; then, if positive skin reactions to mold were obtained, mold extracts were added to the treatment. The same was true of asthmatic patients with indefinite seasonal symptoms, with or without pollen reactions. Our object was to determine how many of these skin reactions had a transferable skin-sensitizing antibody, which patients had molds in their environment, and whether these molds were the same as those they were sensitive to on cutaneous testing.

The patients studied in this series consisted of 123 children and 117 adults. They were all allergic to inhalant substances and were tested routinely to the following molds: *Alternaria, Aspergillus, Hormoden-*

dron, Penicillium, Mucor, and yeast. Intracutaneous tests were done with solutions of 100 and 1,000 protein nitrogen units, and twenty-eight selected cases giving marked positive cutaneous tests were tested ophthalmically with extracts of 5,000 unit strength.

PREPARATION OF EXTRACT

The mold extracts were made in the laboratories of the New York Post-Graduate Hospital in the following manner. They were grown in dextrose broth (4 per cent crude dextrose, 1 per cent peptone with a pH of 5 to 5.5). After a thick mat of mold was obtained, it was washed with buffered saline and killed with 95 per cent alcohol. The mold was then dried in a desiccator for a week, ground in a mortar, and tested for sterility. An extract of 3 per cent by weight of mold powder with buffered saline was made and tested for sterility, and protein nitrogen was determined.

RESULTS OF TESTING

In this paper, we concerned ourselves chiefly with *Alternaria* and the number of reactions to it. In a series of 240 cases suffering from inhalant allergy, thirty patients gave marked skin reactions to *Alternaria* in dilutions of either 100 or 1,000 units, and thirty-six gave moderate reactions. On a percentage basis, 27.5 per cent gave moderate or marked reactions on intracutaneous testing. However, actually only 12.5 per cent gave really marked cutaneous reactions.

TABLE I

INCIDENCE OF SKIN REACTIONS TO AIR-BORNE MOLDS

MOLDS	NUMBER OF PATIENTS	MODERATE REACTIONS		MOD.-MKD. MARKED REACTIONS	
		NO.	PERCENTAGE	NO.	PERCENTAGE
Alternaria	240	36	15	30	12.5
Penicillium	235	17	7.2	10	4.2
Hormodendron	238	34	14.3	4	1.7
Mucor	140	3	2.1	3	2.1
Yeast	210	16	7.6	4	1.9
Aspergillus	240	23	9.6	3	1.2

The other molds gave the results recorded in Table I. *Aspergillus* gave marked skin reactions in three cases (1.2 per cent) and moderate reactions in 23 (9.6 per cent). *Mucor* reactions were marked in three, and moderate in three (2.1 per cent). *Penicillium* gave marked reactions in ten cases (4.2 per cent), and moderate ones in seventeen (7.2 per cent). Yeast reactions were marked in four (1.9 per cent), and moderate in sixteen (7.6 per cent).

Of the 240 patients tested with *Alternaria,* twenty-five (10 per cent) gave reactions to other molds, with a positive reaction to *Alternaria.* The incidence of positive cutaneous tests to mold in children and adults

TABLE II

INCIDENCE OF MOLD REACTIONS IN ADULTS AND CHILDREN

MOLDS	TOTAL TESTED	NUMBER OF ADULTS TESTED	NUMBER OF CHILDREN TESTED			MODERATE REACTIONS	MOD.-MKD. MARKED REACTIONS
Alternaria	240	117	123	A	No.	18	15
					%	15.4	12.8
				C	No.	18	15
					%	14.6	12.2
Penicillium	235	117	118	A	No.	14	9
					%	12.0	7.6
				C	No.	3	1
					%	2.5	.9
Hormodendron	238	115	123	A	No.	21	3
					%	18.2	2.6
				C	No.	13	1
					%	10.5	.8
Mucor	140	48	92	A	No.	2	3
					%	4.3	6.3
				C	No.	1	0
					%	1.1	0
Yeast	210	93	117	A	No.	8	1
					%	8.6	1.1
				C	No.	8	3
					%	6.8	2.5
Aspergillus	240	117	123	A	No.	16	3
					%	13.6	2.5
				C	No.	7	0
					%	5.7	0

is shown in Table II. It is noticeable that in this group the number of marked reactions to *Alternaria* were the same in both children and adults, namely, 12 per cent.

RESULTS OF OPHTHALMIC TESTS, PASSIVE TRANSFER TESTS, AND INSUFFLATION

A selected group of twenty-eight patients giving moderate to marked positive skin reactions were tested ophthalmically with extract containing 5,000 units, and they also had passive transfer studies done. Out of the series of twenty-eight who gave moderate to marked cutaneous reactions to *Alternaria*, eighteen gave positive transfer tests, and twelve had positive eye tests; that is, twelve out of two hundred forty patients were sensitive to *Alternaria*. When the eye tests were positive, the transfer was always positive, but in six cases skin-sensitizing antibodies were demonstrable without positive eye tests. Insufflation was done with *Alternaria* spores. It was found that inhalation with plates with pure cultures of *Alternaria* beneath a patient's nose caused no reaction. When, however, spores were placed on an applicator and applied to the turbinates, a positive nasal response with edema and sneezing was elicited in all patients having positive eye tests. These findings are shown in Table III.

TABLE III

CORRELATION OF DIRECT TESTS, PASSIVE TRANSFER, MUCOUS MEMBRANE TESTS, AND CONTACTS

PATIENT		ALT.	HORMODENDRON	MUCOR	YEAST	PENICILLIUM	ASPERGILLUS	EYE TEST	NOSE TEST	CLINICAL SYNDROME	CONTACT AS SHOWN BY PLATE STUDY OF HOME
G. P.	PK*	mod.-mkd.	0	0	0	0	0	0	0	Hay fever	*Alternaria* neg.
	P†	mkd.	0	0	0	0	0				
D. W.	PK	mod.-mkd.	sl.	0	sl.	sl.	0	+	+	Hay fever; asthma	*Alternaria* pos.
	P	mod.-mkd.	sl.	0	mod.-mkd.	sl.	sl.				
I. B.	PK	mod. +	0	0	0	0	0	+	+	Vasomotor rhinitis	*Alternaria* pos.
	P	mod. +	sl.	mod.	mkd.	0	mod.				
J. A.	PK	0	0	0	0	0	0	0	0	Vasomotor rhinitis	*Alternaria* neg.
	P	mod.-mkd.	0	sl.	sl.	sl.	0				
Mrs. D.	PK	mod. +	0	0	0	0	0	+	+	Hay fever	*Alternaria* neg.
	P	mod.-mkd.	mod.-mkd.	0	0	0	0				
Mr. W.	PK	mod. +	0	0	0	0	0	+	+	Infectious asthma	*Alternaria* neg.
	P	mkd.	0	0	0	0	mod.				
Mr. D.	PK	mkd.	0	0	0	0	0	+	+	Inhalant asthma	*Alternaria* neg.
	P	mod. +	mod.	mod.	mod.	mod.	mod.				
R. S.	PK	mod.	sl.	0	0	0	0	0	0	Hay fever; asthma	*Alternaria* pos.
	P	mkd.	mod.	0	mod.	sl.	mod.				
Mr. H.	PK	0	0		0	0	0	0	0	Infectious asthma	*Alternaria* pos.
	P	mkd.	mod.		0	mod.	sl.				
J. Z.	PK	mod.	0	0	0	0	0	0	0	Hay fever; asthma	*Alternaria* neg.
	P	mod.-mkd.	sl.	0	sl.	sl.	0				
J. C.	PK	mod.	0	0	0	0	0	+	+	Hay fever; asthma	*Alternaria* neg.
	P	mkd.	0	0	sl.	0	0				
S. G.	PK	sl.	0	0	0	0	0	0	0	Vasomotor rhinitis	*Alternaria* neg.
	P	mod.-mkd.	sl.	sl.	mod.	mod.	0				
B. I.	PK	mod.	0	0	0	0	0	+	+	Hay fever; asthma	*Alternaria* pos.
	P	mod.	0	0	0	0	0				

*PK, Prausnitz-Küstner reaction.

†P, Patient.

O. D.	PK P	mod. mkd.	0 mod.	sl. sl.	sl. mod.	0 sl.	sl. sl.	+	+	Timothy asthma	*Alternaria* pos.
F. D.	PK P	mod. mod.-mkd.	0 0	0 0	0 0	mod. 0	0 0	Pen. – Alt. +	Pen. – Alt. +	Vasomotor rhinitis	*Alternaria* pos.
F. G.	PK P	sl. mod.	0 mod.	0 0	0 mod.	0 0	0 mod.	0	0	Hay fever; asthma	*Alternaria* neg.
H. G.	PK P	sl.-mod. mod.	0 0	0 sl.	0 0	0 mkd.	sl. mod.	Alt. – Pen. –	Alt. – Pen. –	Infectious asthma	*Alternaria* neg.
M. J.	PK P	mkd. mkd.	0 sl.	0 sl.	0 sl.	0 sl.	0 sl.	0	0	Infectious asthma	*Alternaria* pos.
H. M.	PK P	0 mkd.	0 mod.	0 0	0 mod.	0 sl.	0 0	0	0	Hay fever; asthma	*Alternaria* neg.
P. L.	PK P	mod.-mkd. mod.	0 0	0 0	0 0	0 0	0 0	0	0	Infectious asthma	*Alternaria* neg.
M. H.	PK P	0 0	0 mod.	0 0	0 sl.	0 0	0 sl.	0	0	Hay fever; Vasomotor rhinitis	*Alternaria* neg.
E. L.	PK P	mod. mkd.	0 sl.	0 sl.	0 0	0 sl.	0 sl.	+	+	Hay fever; asthma	*Alternaria* pos.
H. P.	PK P	sl. mod.	0 0	0 0	0 0	0 0	0 0	0	0	Infectious asthma	*Alternaria* neg.
Mrs. L.	PK P	mkd. mkd.	0 sl.-mod.	0 mod.	0 0	0 sl.-mod.	0 0	+	+	Hay fever; asthma	*Alternaria* neg.
Mr. M.	PK P	0 mkd.	0 0	0 0	0 0	0 0	0 0	0	0	Hay fever	*Alternaria* neg.
Mr. G.	PK P	mkd. mkd.	0 mod.	0 0	0 mod.	0 sl.-mod.	0 0	+	+	Hay fever	*Alternaria* neg.
Mr. E.	PK P	0 mkd.	0 mod.	0 0	0 0	0 0	0 0	0	0	Hay fever	*Alternaria* neg.
Mr. L.	PK P	0 mod.-mkd.	0 mod.-mkd.	0 mod. +	0 mod.	0 mod. +	0 mod.-mkd.	0	0	Hay fever; asthma	*Alternaria* neg.

SEROLOGIC STUDIES

Serum was taken from six sensitive *Alternaria* patients with positive skin, eye, and insufflation tests. Quantitative neutralization of *Alternaria*-sensitive sera was carried out to determine the relative neutralization capacity of *Alternaria* extract. The technique was that outlined by Cooke[15] and his co-workers. The sera were mixed with equal parts of *Alternaria* extract in varying strengths, as shown in Table IV, in sterile tubes, and were incubated overnight in the icebox. Intradermal skin sites, each containing 1 c.c. of such mixture, were then made. After forty-eight hours, when all reactions or irritations had subsided, the sites were tested with .025 c.c. of *Alternaria* extract, containing 17,000 units per cubic centimeter. The neutralization is shown in Table IV and occurs in mixtures of 5,000 units or more. One serum, sensitive to *Alternaria*, timothy, and ragweed, was incubated with *Alternaria*, 17,000 units. Sites were put in normal skin as described above and then tested forty-eight hours later with the respective antigens, as shown in Table V. *Alternaria* will neutralize only against itself, and not to timothy or ragweed; therefore, it is a specific immunologic substance.

TABLE IV

NEUTRALIZATION OF SERA

SERUM OF PATIENT	L	W	G	WE	DIT	DA
+ *Alternaria*, 100	4+	2+	4+	2+	2+	3+
+ *Alternaria*, 1,000	4+	1+	3+	2+	2+	2+
+ *Alternaria*, 5,000	2+	neg.	2+	neg.	neg.	neg.
+ *Alternaria*, 17,000	neg.	neg.	1+	neg.	neg.	neg.
+ Saline	4+	3+	4+	4+	3+	4+

Each site was tested with *Alternaria* extract, 17,000.

TABLE V

CROSS NEUTRALIZATION

	PATIENT, MRS. L.		REACTION
1			
a	Serum + *Alternaria*, 17,000	Tested with *Alternaria*, 17,000	0
b	Serum + *Alternaria*, 17,000	Tested with Ragweed, 20,000	4+
c	Serum + *Alternaria*, 17,000	Tested with Timothy, 18,000	3+
2			
a	Serum + Ragweed, 20,000	Tested with Ragweed, 20,000	1+
b	Serum + Ragweed, 20,000	Tested with *Alternaria*, 17,000	3+
c	Serum + Ragweed, 20,000	Tested with Timothy, 18,000	3+
3			
a	Serum + Timothy, 18,000	Tested with Timothy, 18,000	0
b	Serum + Timothy, 18,000	Tested with *Alternaria*, 17,000	3+
c	Serum + Timothy, 18,000	Tested with Ragweed, 20,000	3+

DISCUSSION

Patients were given Sabouraud's plates to be exposed at home, and in only seven cases of twenty-eight did *Alternaria* molds to which they were sensitive grow, as shown in Table III. The plates were exposed in

the homes of the patients in New York and New Jersey between the months of October and March. Of course, during this time no *Alternaria* spores are found in the air.

From the observations above, it is seen that sensitization to fungi is a real immunologic entity, but one which occurs relatively infrequently in this locality. Of twenty-eight cases giving positive cutaneous reactions to *Alternaria*, in only twelve was *Alternaria*, which is the most common offender, a clinical factor. These twenty-eight gave the best reactions and were selected from a group of sixty-six as the best to study serologically.

It is obvious that our observations and conclusions are true only for patients living in New York and New Jersey. In these localities the mold counts have never been high, and that may well account for the small incidence of sensitivity in our group. On the other hand, no studies have been carried out routinely on patients living in areas where the mold count is high, to see how many of them were constitutionally sensitive by blood, eye, and insufflation testing. It may well be that figures in these localities might be higher.

The fact that we have not encountered a positive insufflation test in the presence of a negative transfer or eye test is significant, and it means that the eye test is an easy check for constitutional sensitivity. It is, therefore, suggested that, before adding any mold extract to a patient's treatment, eye tests be used as an indicator for treatment.

CONCLUSIONS

Of 244 cases, sixty-six (27.5 per cent) gave positive skin reactions to *Alternaria*. Twelve of a series of twenty-eight selected cases with positive skin reactions in both children and adults were found to be constitutionally sensitive.

Eye tests were positive when passive transfer and insufflation tests were positive.

Eye testing is an easy check on the need for therapy.

Exposed plates showed that seven of twenty-eight patients had molds in their homes to which they were skin-sensitive.

Neutralization studies show that *Alternaria* sensitivity can be marked.

Cross neutralization shows it to be specific, as neither timothy nor ragweed will neutralize against *Alternaria* in the specific serum studied.

REFERENCES

1. Van Leeuwen, W. S.: Bronchial Asthma in Relation to Climate, Proc. Roy. Soc. Med. **17**: 19, 1924.
2. Cadham, F. T.: Asthma Due to Grain Rust, J. A. M. A. **83**: 27, 1924.
3. Hopkins, J. G., Benham, R. W., and Kestin, B. M.: Asthma Due to a Fungus Alternaria, J. A. M. A. **94**: 6, 1930; Sensitization to Saprophytic Fungi in a Case of Eczema, Proc. Soc. Exper. Biol. & Med. **27**: 342, 1929-1930.
4. Bernton, H. S.: Asthma Due to a Mold, Aspergillus Fumigatus, J. A. M. A. **95**: 189, 1930.

5. Flood, C. A.: Observations on Sensitivity to Dust Fungi With Patients With Asthma, J. A. M. A. **96**: 2094, 1931.
6. Jimenez-Diaz, C., Sánchez Cuenca, B., and Puig, J.: Climatic Asthmas, J. ALLERGY **3**: 396, 1932.
7. Towey, J. W., Sweeney, H. C., and Huron, W. H.: Severe Bronchial Asthma Apparently Due to Fungus Spores Found in Maple Bark, J. A. M. A. **99**: 453, 1932.
8. Balyeat, R. M.: Comparative Pollen, Mold, Butterfly, and Moth Emanation Content of the Air, J. ALLERGY **3**: 207, 1932.
9. Feinberg, S. M.: Mold Allergy—Its Importance in Relation to Asthma and Hay Fever, Wisconsin M. J. **34**: 204, 1935.
10. Lamson, R. W., and Rogers, E. L.: Skin Hypersensitivity to Molds, J. ALLERGY **7**: 582, 1936.
11. Brown, G. T.: Hypersensitiveness to Fungi, J. ALLERGY **7**: 455, 1936.
12. Schonwald, M.: Allergic Molds—Pacific Northwest, J. ALLERGY **9**: 175, 1938.
13. Fraenkel, E. M.: Molds and Asthma, Brit. M. J. **2**: 68, 1938.
14. Pratt, H. N.: Seasonal Aspects of Asthma and Hay Fever in New England With Special Reference to Mold Spores, New England J. Med. **219**: 782, 1938.
15. Cooke, R. A.: Clinical and Serological Relationship of Grass and Low Ragweed, J. ALLERGY **6**: 311, 1935.

A CLINICAL COMPARISON OF EPINEPHRINE IN OIL AND EPINEPHRINE IN GELATIN

MORRIS KALMON, M.D.
AKRON, OHIO

THE use of epinephrine in a slowly absorbed medium for clinical use was first attempted by Strauch,[1] who attempted to delay the absorption of epinephrine and other drugs by preparing emulsions of these substances. Alvis,[2] in 1934, made a 2 per cent preparation in phenolated tragacanth jelly for ophthalmologic use, which, it was claimed, had better preservative qualities and remained in contact with the conjunctiva longer than the instilled drop. The vehicle was then changed to an oxycholesterol petroleum ointment base, which has the advantage of mixing better with the tears than the original menstruum.

In 1938, Keeney[3] submitted a preliminary report on what he called "slow epinephrine," in which 2 mg. of powdered epinephrine base were added to 1 c.c. of purified, sterilized olive oil and this mixture was subjected to supersonic radiations for seven minutes. He later changed the menstruum to peanut oil, because he felt that this was less irritating than olive oil. This preliminary report was followed approximately one year later by a further report[4] in which it was definitely shown that this preparation had a number of advantages over the ordinary 1:1,000 solution, making its use advisable in the treatment of asthmatic attacks.

During the interim, however, between the publication of Keeney's findings and the preparation of this product commercially, Spain and others[5] introduced another type of slowly absorbed epinephrine, with gelatin as the medium for retarding absorption.

In these reports, both Keeney and Spain cited experiments to prove that these vehicles were absorbed into the general system without harmful effects.[6-9] Spain, moreover, claimed the advantage for gelatin in that it was nonantigenic.

Since Spain's mixture was considered the simpler of the two for preparation, we prepared approximately 150 c.c. of this base. Results were gratifying, but when the epinephrine in oil was made commercially available, we proceeded to use both types of mixtures in the same patients in order to make a comparative clinical study. The effects on twenty-two patients with a total of 225 injections of both types of preparations were thus studied. One hundred twenty-five cubic centimeters of the epinephrine-gelatin mixture and 100 c.c. of the "slow epinephrine" were used. The greatest number of injections given to any patient to

Read before the Cleveland Allergy Society, Jan. 30, 1940.

date is thirty, and the smallest, one. The remainder of the patients, except for two others (who had twenty-four and twenty) averaged between eight to ten injections, administered as the occasion arose. Of these patients, three may be disposed of since they had but one injection each. In the remaining patients, we were able to study the effects of both types of preparations after repeated injections. Only one of these patients was hospitalized, and, therefore, many of these observations are based upon the patients' own statements.

Observations under consideration were as follows: (1) speed of initiation of action; (2) effectiveness and duration of relief; (3) tenderness or irritation at site of injection; (4) tremor and palpitation; (5) other side reactions and (6) unusual reactions.

Speed of Initiation of Action.—Both types acted equally with noticeable effect beginning within from twenty to thirty minutes after administration. In this respect, however, the gelatin preparation has an advantage in that a small amount of the ordinary 1:1,000 epinephrine solution may be drawn into the syringe for simultaneous injection with the gelatin mixture whenever a speedier action is desired. This plan is obviated when using "slow epinephrine," since Keeney advised the use of a dry syringe for injection; in order to obtain quick action, two injections become necessary.

Effectiveness and Duration of Relief.—Not all patients obtain relief with this treatment, and our observations coincide with those of Spain; namely, if epinephrine, 1:1,000, will relieve an attack, the slowly absorbed mixtures will also, but if no relief is obtained with the ordinary solution of 1:1,000, then no relief may be expected with the other types, even if given in amounts up to 2 c.c. In one case 2 c.c. of the peanut oil preparation was used, and in another three attempts were made on successive days to ease an asthmatic attack with the gelatin preparation, with no results. Epinephrine, 1:1,000, also gave no relief in this case. In one patient, epinephrine in gelatin relieved attacks on two successive days, when the "slow epinephrine" failed to. We are at a loss to explain this finding and can give as a possible explanation only the fact that the epinephrine in oil had solidified while in the refrigerator, and although reliquified under running hot water, a fine precipitate which could not be dispersed remained in the bottom of the ampoule. A portion of the epinephrine base thus may have been left in the vial when the liquid was drawn into the syringe. At other times, when the "slow epinephrine" was given this patient, good results were obtained, comparable to that of the gelatin preparation. In all the other occasions where either type of mixture was used, equal results were noted in so far as effectiveness in abating the asthma was concerned.

Duration of Relief.—In this regard we have observed that the "slow epinephrine" is superior. Keeney observed that the duration of relief in his patients had been from nine to sixteen hours, and Spain has

claimed practically the same for his preparation; yet we have noticed that, under similar conditions, there was an average of at least two hours' longer relief with the oily preparation. The severity of the attack appeared to affect the duration of relief, in that the more severe the attack, the shorter the period of relief. When effective, the "slow epinephrine" gave relief from nine to fourteen hours, while the epinephrine-gelatin mixture relieved for twelve hours at the longest, with a minimum of six hours.

Tenderness at Site of Injection.—Keeney recommended that "slow epinephrine" be given intramuscularly, but Spain advocated subcutaneous injections, claiming that this was another advantage for his preparation. When, however, Keeney's preparation appeared on the market, one company stated that it could be administered either subcutaneously or intramuscularly, while another firm gave instructions that this preparation was only to be used intramuscularly. We used both routes and when we failed to notice any undue irritation, we adopted the subcutaneous method.

It soon became apparent that irritation was more marked following the use of the gelatin mixture, and, although not severe with either type, the tenderness following the use of the "slow epinephrine" lasted about twenty-four hours, whereas with gelatin it remained for approximately thirty-six hours. In several instances, the tenderness would be present for longer periods, but these occasions were exceptional. This condition, however, did not preclude the use of these preparations over a continued period of time. In one patient these mixtures were given subcutaneously in alternate arms, the gelatin mixture in the left arm, and the "slow epinephrine" in the right. In one month, twelve injections of each type had been given. The left arm, in which the gelatin preparation had been administered, appeared red, somewhat tender, and had a rather glazed, shiny appearance. Although nodules appeared in this arm at the sites of three injections, the patient did not complain of any undue amount of tenderness, nor did she refuse further injections in that arm, because of the pain. Each of these nodules remained for a period of ten days. There were no nodules in the other arm. Nodules were also noted following twenty other injections of the gelatin mixture in other patients, which remained for a period of from seven to ten days, but we observed none following the use of the "slow epinephrine."

Tremor and Palpitation.—Palpitation occurred in five patients following the injections. This symptom usually occurred shortly before, or simultaneously with, the beginning of relief of the attack. The frequency of occurrences was equal with both types. In one patient, these symptoms occurred after 1 c.c. of each type had been administered, on different occasions, both hypodermically, but when the dose was reduced to 0.75 c.c., this symptom no longer occurred. Another patient was a child 3 years of age, an asthmatic, who received a total of four injec-

tions of 0.50 and 0.35 c.c. of each type of preparation, the gelatin mixture subcutaneously, and the oily preparation intramuscularly. Palpitation followed only the larger doses, with no side effects after the dose was reduced.

With the other patients, our experience was similar to that stated above, in that where one type causes palpitation, the other type will also, if given in the same dose. In no case was the palpitation marked, and no dyspnea was noted. Tremor was seen in only one patient, who was given a dose of 0.75 c.c. of the gelatin mixture. None of the patients who exhibited these reactions following the use of the preparations showed any apprehension or nervousness which could at all compare to that exhibited when a larger dose (0.75 to 1.00 c.c.) of the ordinary epinephrine is administered.

Other Side Reactions.—Headache, nausea, vomiting, nervousness, insomnia, perspiration, and cyanosis were reported by authors[10] who have studied these preparations. We have noted only two of these manifestations, headache, and cyanosis, and in but two instances, once when 2 c.c. of the oily preparation was administered, and once in the instance to be described below. The cyanosis in the first case lasted approximately forty-five minutes, while the headache remained for approximately six hours.

Unusual Reactions.—With the advent of the slow epinephrine, the question of peanut oil sensitivity naturally presented itself. Keeney stated that, in over 2,000 injections, there was only one suspicious allergic reaction to peanut oil. Other writers have reported some unusual reactions which, however, apparently were unrelated to peanut oil sensitivity. Cohn[11] reported four patients with symptoms of cyanosis, dyspnea, vomiting, chills, vesicular urticaria, swelling, and edema of the forearm.

We have had two unusual reactions, both in the same patient, one following an injection of the oily preparation and occurring about three minutes after administration. The injection had been given subcutaneously in the arm at the usual site, and, in the time stated, the entire limb from the site of the injection down to all the finger tips became blanched. The patient did not complain of pain, and after being observed for thirty minutes, was sent home. As soon as he arrived there, he called the office, stating that his limb was paralyzed and rather painful. We advised massage and heat in order to increase circulation. Within half an hour the pain was receding and he was beginning to regain the use of his arm again. Six hours after the injection the arm became completely normal. When seen, three days later, there was an area of ecchymosis about the size of a silver dollar around the site of the injection. There were no systemic symptoms. Apparently, the medication had entered a small blood vessel.

The second reaction also occurred very rapidly following the use of the epinephrine-gelatin mixture. In this instance, "slow epinephrine," which had been kept in the refrigerator and had solidified, was injected first, after being warmed, without any definite relief after 30 minutes. Having seen this occur twice previously in the same patient, we then proceeded to administer the gelatin preparation. Immediately following this second injection, the patient became cyanotic and doubled over, complaining of severe gastric cramps and nausea. Palpitation and dyspnea were also present, although the palpitation was not marked (pulse 124). Within five minutes the patient had completely recovered from his pain and nausea, although the cyanosis lasted for another twenty minutes, and the increased pulse gradually lessened over a period of three hours. He did, however, develop a severe headache for five hours. This patient, who had been suffering from moderately severe daily asthmatic attacks, had no further symptoms for six days following this injection, after which time the asthma reappeared.

DISCUSSION

Both types of preparations have been a very beneficial addition to our armamentarium of drugs used in the treatment of acute allergic attacks. It is difficult to make a choice between the two, since each has its advantages. For example, the oily preparation apparently is not best suited for use by the patient at home since a dry sterile syringe is advocated, and this is very inconvenient for a lay person to attain. On the other hand, the epinephrine-gelatin mixture should be kept solidified, and since it melts at ordinary room temperature, this type is not best suited for the general practitioner who does not have a refrigerator in his office. Again, the gelatin preparation may be combined with the ordinary 1:1,000 solution for speedier action, when so desired, while the oily preparation may not. Another important consideration is the possibility of peanut oil sensitivity.

Despite all the advantages listed for the gelatin preparation, our preference has been the oily mixture, because, first, it is less irritating and painful, and, second, because of the few hours' longer relief that it gives. Another point which has influenced us has been that the patients themselves, when allowed to express their preference, have, without exception, requested the oily preparation.

SUMMARY

1. Two types of slowly absorbed epinephrine preparations are compared as to their relative clinical merits.

2. The advantages and disadvantages of each are reported.

3. Two unusual reactions following the injections of these preparations are described.

REFERENCES

1. Strauch, C. B.: Repository Injections: How to Obtain Lasting Effects With Injected Water-Soluble Medicaments Such as Insulin and Epinephrine, J. A. M. A. **92**: 1177, 1929.
2. Alvis, B. Y.: Suprarenin Jelly, Tr. Am. Acad. Ophth. **39**: 403, 1934.
3. Keeney, E. L.: A Slowly Absorbed Epinephrine Preparation; Preliminary Report, Bull. Johns Hopkins Hosp. **62**: 227, 1938.
4. Keeney, E. L., Pierce, J. A., and Gay, L. N.: Epinephrine in Oil, Arch. Int. Med. **63**: 119, 1939.
5. Spain, W. C., Strauss, B. A., and Fuchs, A. M.: A Slowly Absorbed Epinephrine-Gelatine Mixture, J. ALLERGY **10**: 209, 1939.
6. Binet, L.: Absorption of Oil Injected Subcutaneously, Bull. et mém. Soc. méd. d. hôp. de Paris **49**: 1458, 1925.
7. Shick, B., Fries, M., Kohn, J., and Cohen, P.: Observations of the Nutritional Effect of Subcutaneous Injections of Oil, Proc. Soc. Exper. Biol. & Med. **21**: 445, 1924.
8. Hogan, J. J.: Intravenous Use of Colloidal (Gelatine) Solutions in Shock, J. A. M. A. **64**: 721, 1915.
9. Freedman, L., and Kramer, E. O.: Diffusion of Non-Electrolytes in Gelatin Gels, J. Am. Chem. Soc. **52**: 1305, 1311, 1930.
10. Murphy, J. A., and Jones, C. A.: Slow Epinephrine in the Treatment of Chronic Asthma, J. ALLERGY **10**: 215, 1939.
11. Cohn, J.: Unusual Reactions to Slow Epinephrine, J. ALLERGY **10**: 459, 1939.

707 SECOND NATIONAL BANK BUILDING

Special Reports

THE PREPARATION OF ACTIVE ALLERGENIC EXTRACTS

A Method for the Prevention of Pigmentary Oxidative Products

Margaret B. Strauss, B.A., and W. C. Spain, M.D.
New York, N. Y.

MANY allergenic substances now in general use are so deeply colored that an intracutaneous test with such material often leaves on the patient's skin a tattoolike mark of more or less permanence. The substances, such as celery, pear, wheat, and white potato, from which some of the darkest extracts are derived, are originally colorless. In the course of our investigations, it became evident that the presence of a reducing substance in the extracting fluid prevented the formation of dark color in an extract (with the exception of dust extracts), and, at the same time, did not interfere with the therapeutic properties.

In earlier studies sodium bisulfite was used as the reducing agent, but it was discarded as it was relatively unstable. However, approximately seventy-five patients were treated in 1939 with pollen extracts made up in a sodium bisulfite extracting fluid, with clinical results quite comparable to those in a control group of patients treated with the regular saline pollen extracts. Sodium formaldehyde sulfoxylate was finally chosen as the reducing substance. It is a combination of sodium bisulfite and formaldehyde. Previous workers have shown that it is quite stable in alkaline solutions, nontoxic even when given in large intravenous doses to human beings, and has some bactericidal action.

The following well-buffered sodium formaldehyde sulfoxylate extracting fluids are used:

1. Diluting and extracting fluid, pH 7.4.
   One liter contains 2.723 Gm. KH_2PO_4 plus 78.68 c.c. 0.2M NaOH plus 10 Gm. sodium formaldehyde sulfoxylate.
2. Concentrated extracting fluid.
   One liter contains 13.61 Gm. KH_2PO_4 plus 393.4 c.c. 0.2M NaOH plus 50 Gm. sodium formaldehyde sulfoxylate.
3. Alkaline extracting fluid, pH 8.5.
   One liter contains 8.06 Gm. H_3BO_3 plus 65 c.c. 1.0N NaOH plus 350 c.c. 0.1N HCl plus 10 Gm. sodium formaldehyde sulfoxylate.

When simultaneous extractions were made in buffered sodium formaldehyde sulfoxylate solutions and either buffered saline, preserving fluid, or alkaline saline solutions, it was found that a much greater protein and nonprotein nitrogen extraction was obtained by the use of buffered sodium formaldehyde sulfoxylate, despite the fact that these extracts were considerably lighter in color. The total nitrogen extracted

Presented at the Annual Meeting of the Society for the Study of Asthma and Allied Conditions, Atlantic City, N. J., May 4, 1940.

From the Division of Allergy, Department of Medicine, New York Post-Graduate Medical School and Hospital, Columbia University.

was also greatly increased so that it could not be argued that the increased protein nitrogen was due to a linkage of nonprotein nitrogen with sodium formaldehyde sulfoxylate to give a phosphotungstic acid precipitable protein.

Buffered sodium formaldehyde sulfoxylate solutions did not detoxify or denature any extracts, but simply prevented oxidation by the presence of the strong reducing agent. Repeated nitrogen determinations on various batches of sodium formaldehyde sulfoxylate have consistently given negative results.

A 3 per cent pollen extraction of low ragweed in Coca's solution gave a 23,000 protein unit extract, with a total nitrogen of 0.57 mg. per cubic centimeter, while a similar extraction in buffered sodium formaldehyde sulfoxylate gave a 31,000 protein unit extract, with a total nitrogen of 0.66 mg. per cubic centimeter. Thus, there is in this instance a 35 per cent increased protein nitrogen extraction with sodium formaldehyde sulfoxylate over the amount extracted in Coca's solution. All extracts have been tested intracutaneously on sensitive patients, with identical results with both extracts. Mixtures of pollen-sensitive serum plus pollen extract have been incubated and tested in the skin of normal recipients. On retest with regular and sodium formaldehyde sulfoxylate extracts, equal neutralization points have been obtained with both extracts, showing that these noncolored extracts are as active as the regular extracts and that the increased amount of protein nitrogen extracted by the buffered sodium formaldehyde sulfoxylate is also active. Were such a largely increased protein nitrogen content inactive, it would be apparent on skin test or neutralization test after dilution to a protein unit equal to that of the regular extract.

So far, the buffered sodium formaldehyde sulfoxylate pollen extracts have been in use in a group of patients for only three months, so that as yet no clinical results are available. However, there have been no irritating reactions of any kind, and retests of 6-month-old buffered sodium formaldehyde sulfoxylate pollen extract gave identical skin tests and neutralization point reactions as did the regular 6-month-old extract.

SUMMARY

It has been possible, by the use of sodium formaldehyde sulfoxylate buffered solutions, to prepare active allergenic extracts with the complete elimination of pigmentary oxidative products.

A larger amount of active material is extracted by use of a buffered sodium formaldehyde sulfoxylate extracting fluid than with the regular extracting fluids now in use, when equal weight by volume extractions are made.

These new extracts give the same skin and serum neutralization point tests as do the regular extracts of the same age.

The buffered sodium formaldehyde sulfoxylate extracts are being investigated over a longer period of time to determine whether or not they will be more stable than the extracts now in general use.

DERMATITIS CAUSED BY CONTACT WITH COPPERWEED (OXYTENIA ACEROSA)

LOUIS SCHWARTZ, M.D., AND LEON H. WARREN, M.D.
WASHINGTON, D. C.

DERMATITIS has been reported from contact with many plants, but there have been no reports in the literature of dermatitis caused by copperweed. Systemic poisoning in animals from grazing on this weed is well known to the United States Department of Agriculture, where investigations to rid grazing areas of copperweed are under way.

Copperweed (*Oxytenia acerosa* Nutt) (Fig. 1) is described by Muenscher[1] as follows: "Stems erect, branched, woody at base, from 1 to 2 M. high, at times leafless and rushlike. Leaves alternate, parted into from three to five linear segments or the upper entire. Heads small, greenish, with five involucral bracts, unisexual, in panicles of spikes; pistillate heads with about five flowers without corolla; staminate heads with from ten to twenty-one flowers. Achenes obovoid, hairy, without pappus. Distribution and habitat: On arid, alkaline soils in foothills and sagebrush plains. Southwestern Colorado, Utah, Arizona, and southeastern California. Conditions of poisoning: Sheep have been poisoned by grazing on the tops of Oxytenia on dry ranges of southern Utah."

CASE REPORT

The patient, a white male aged 55 years, was a plant chemist working on the investigation of copperweed by the United States Department of Agriculture. His past medical history was irrelevant, with the possible exception of gastrointestinal disturbances following the ingestion of veal and eggs. He consulted the authors for treatment of an acute dermatitis involving the entire dorsum of the right hand and wrist (Fig. 2) and a less severe and extensive involvement of the left which he suspected might have been caused by contact with crown of thorns *(Euphorbia splendens)*. He suspected this plant because he had picked up in his ungloved right hand the remains of a potted *Euphorbia splendens* which had been dropped accidentally, and because the *Euphorbiaceae* (order of *Geraniales*) are notorious causes of dermatitis. This particular species *(splendens)* has long, sharp thorns and exudes a sticky, thick, milky sap. Although eleven species of the family of *Euphorbiaceae* have been reported as having caused dermatitis, *Euphorbia splendens* is not included.

The patient brought us a piece of the fresh crown of thorns for patch testing, but stated that he believed the sap of this plant to be a primary skin irritant (a substance which will cause contact dermatitis in by far the large majority of persons). For this reason, we did not perform a patch test with it, fearing that such a test might cause a violent reaction and an exacerbation of the already severe dermatitis of his hand.

However, a volunteer submitted to patch testing with a cut piece of the fresh stalk of the plant, from which the sap exuded. There was no reaction at the

From the Office of Dermatoses Investigations, United States Public Health Service, Washington, D. C.

end of twenty-four hours. This test definitely proved that the plant is not a primary skin irritant and made patch testing of the patient with this plant practical.

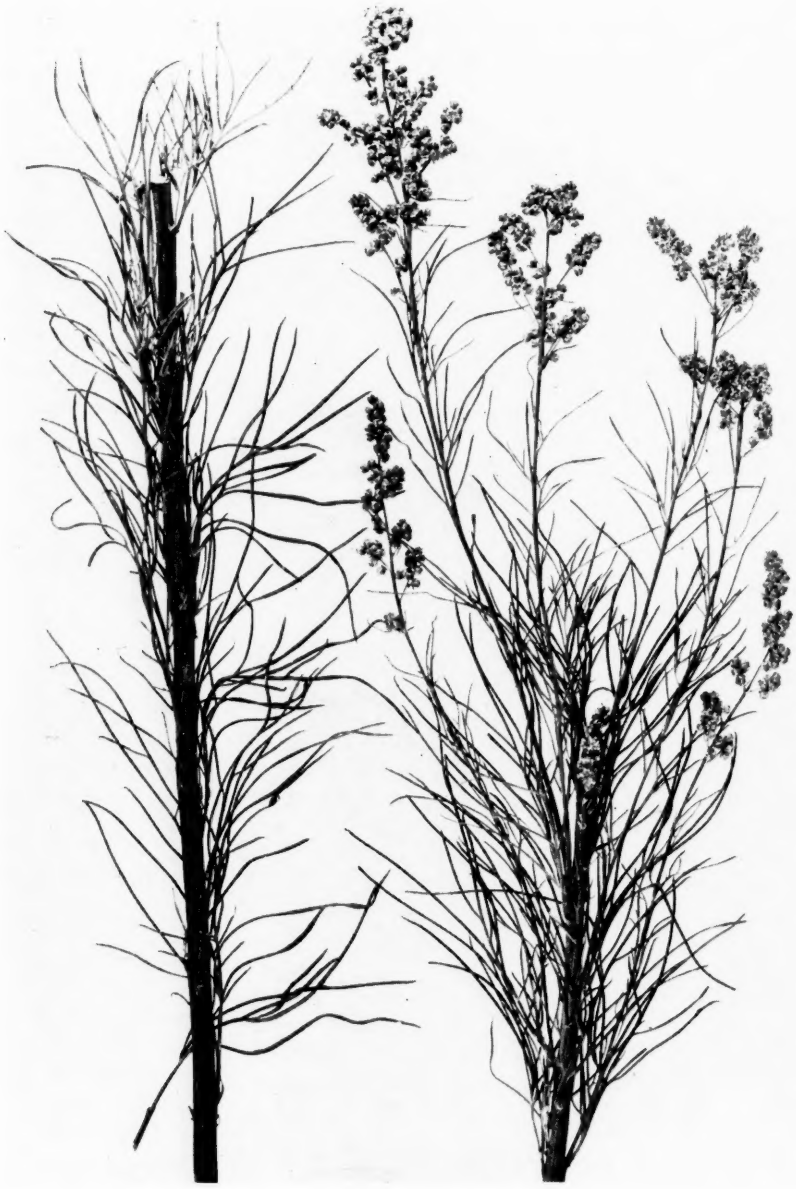

Fig. 1.—Copperweed (*Oxytenia acerosa* Nutt).

In the meantime, it was ascertained that the patient had handled many other plants, six of which (including the crown of thorns) he had been in contact with a week or more before the eruption developed. He was told to bring us the six plants, and he returned the following week with them. They were: copperweed *(Oxy-*

tenia acerosa Nutt); pigweed (*Amaranthus retroflexus*); milkweed (*Asclepias labriformis*); crown of thorns (*Euphorbia splendens*); Chinese scholar tree (*Sophora japonica*); and poinsettia (*Euphorbia pulcherrima*).

Fig. 2.—Dermatitis caused by copperweed.

After four weeks of mild local treatment, the contact dermatitis of the right hand had subsided sufficiently to risk a flare-up by patch testing with the suspected plants. Patch tests were done on the patient's back with small portions of the ground, dried plants moistened with water, except in the case of the crown of thorns in which the freshly cut stalk and sap were used. When the patch tests were removed at the end of nineteen hours, a faint erythematous reaction was

present at the sites of the patches of the first four plants listed above. The erythema was most marked at the site of the pigweed patch test, but even there it was not more than a simple localized erythema and not of sufficient severity to be consistent with the degree of dermatitis that had been present on the patient's hand. However, the dermatitis of the hand flared up, suggesting that one or more of the four plants giving positive patch tests was the cause of the original dermatitis. The patient had collected pigweed daily for a period of two weeks, but had not come into contact with it for one month prior to the outbreak of dermatitis. He was requested to return the following day for observation of possible delayed reactions. Upon his return the next day, all signs of reaction had disappeared from all patch test sites with the exception of the one to copperweed, which had become edematous and vesiculopapular and had increased

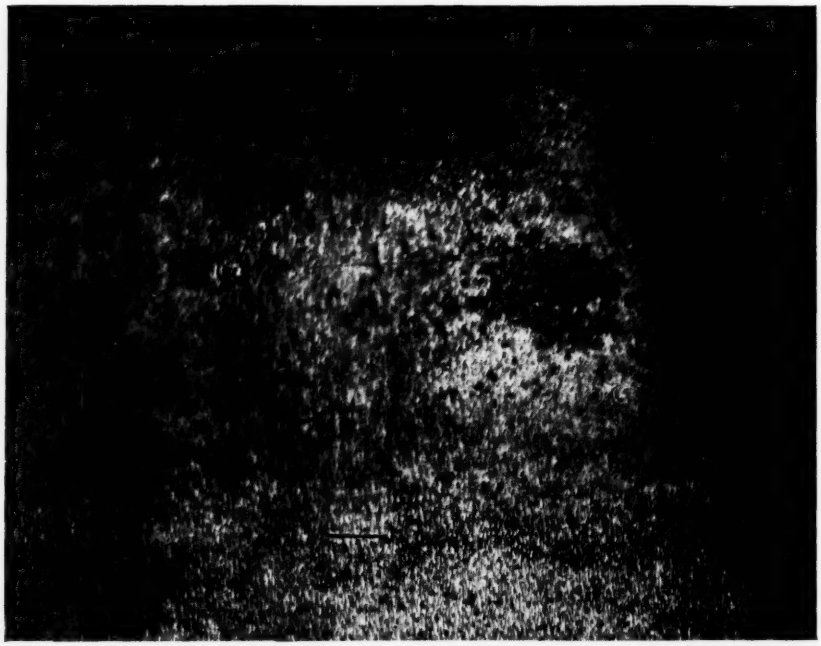

Fig. 3.—Patch test with copperweed.

from 6 mm. to 2.5 cm. in diameter (Fig. 3). This eczematized patch test reaction to copperweed persisted for over three weeks. The eczematization of the patch test site, accompanied by the exacerbation of dermatitis and the transient nature of the slight reaction to the other three plants, indicated that the copperweed was the principal cause of the dermatitis. The patient now stated that he had been handling copperweed for a number of months, but had not suspected it as the cause of his dermatitis because copperweed had never before been reported to have caused dermatitis.

In an attempt to determine what principle in the copperweed caused the patient's hypersensitivity, four extracts of the plant were made as follows:

One gram of the dried plant (collected Aug. 19, 1938, at Ferron, Utah, and Sept. 7, 1938, in Garfield County, Utah) was thoroughly ex-

tracted by successive portions of ether in the cold. The ether was filtered off and allowed to evaporate at room temperature. The thin film of green resin remaining was mixed with 3 c.c. of olive oil and bottled for testing.

The extracted plant was then dried in air and again thoroughly extracted with 95 per cent ethanol. This extract was filtered off and allowed to evaporate at room temperature. The yellowish resin residue was mixed with 3 c.c. of olive oil and bottled for testing.

The residue after this treatment was mixed now with 45 c.c. of cold distilled water, allowed to stand two days, and filtered. On account of evaporation, the filtrate was made up to 45 c.c. by adding water. Five cubic centimeters of 95 per cent ethanol was added as a preservative, and the extract was bottled for testing.

One gram of nonextracted plant was mixed with 45 c.c. of distilled water and allowed to stand two days. The water extract was then filtered and made up to 45 c.c. with distilled water; 5 c.c. 95 per cent ethanol was added as a preservative, and the extract was bottled for testing.

The following skin tests with these extracts were performed on the patient:

Skin Test 1.—One drop of the alcohol extract made after ether extraction of the copperweed was applied to the skin of the patient's back. Although there was a slight erythematous reaction at the end of twenty-four hours, this reaction had disappeared entirely at the end of the following day.

Skin Test 2.—One drop of the ether extract of copperweed was applied to the skin of the patient's back and also to the skin of a control subject. Both tests were negative at the end of twenty-four hours.

Patch Test 3.—Four thicknesses of gauze were moistened with the 2 per cent water extract of the remains of the plant after ether and alcohol extraction and applied as a patch test to the patient's back. There was no reaction to this test at the end of twenty-four hours.

Patch Test 4.—Four thicknesses of gauze were moistened with the 2 per cent water extract of the whole plant and applied as a patch test to the patient's back. There was no reaction at the end of twenty-four hours.

Since there was a positive, though transient, skin reaction to the alcohol extract (after ether extraction) but not to the ether extract, it seems that the toxic principle is alcohol-soluble and ether-insoluble. Since the ether- and alcohol-soluble fractions of 1 Gm. of the plant were dissolved in 3 c.c. olive oil, the concentration of irritant agent in the skin tests with the above two extracts was only about one-third of that occurring in the copperweed; in patch tests 3 and 4 it was only one-fiftieth of that occurring in the copperweed. This may account for the

failure to obtain a more pronounced reaction from test 1 and any reactions from the others. It was impossible to recall the patient and to obtain more of the copperweed for repetition of the patch tests with stronger concentrations of the extracts.

Although the dermatitis improved slowly under mild treatment, it took several months before it entirely disappeared.

SUMMARY

A severe case of a persistent dermatitis caused by copperweed in a sensitized person is reported.

Patch tests with copperweed were positive.

REFERENCE

1. Muenscher, Walter C.: Poisonous Plants of the United States, ed. 1, New York, 1939, The Macmillan Co., p. 222.

ALLERGY TO DIGITALIS

Report of a Case

Robert V. Cohen, M.D., and Maurice L. Brodsky, M.D.
Philadelphia, Pa.

CONSIDERING the wide use of digitalis and its derivatives in clinical medicine, the paucity of reports of allergic manifestations is rather surprising. Cushny[1] and Bastedo[2] do not mention allergy among the complications of digitalis administration. Sollmann[3] speaks of "a few cases of urticaria and scarlatiniform rashes after digipuratum and digalen." Luten[4] writes that no authentic instance of digitalis allergy has come to his attention, and Coca[5] fails to mention digitalis allergy.

An interesting case is reported by Heydner.[6] His patient was given 6 c.c. of digalen and subsequently developed bradycardia, pallor, vomiting, hiccough, and, on the sixth day, a scarlatiniform exanthem which persisted for forty-eight hours. These reactions evidently represented a combination of drug intolerance and allergy. Urbach[7] mentions a pharmacologist who suffered asthmatic attacks only when she worked with powdered digitalis. Other powdered drugs caused no asthmatic attacks. Brandt[8] reported a patient who developed an eczema-like exanthem whenever she took digitalis.

We have inquired of a number of cardiologists and allergists regarding their experience with allergy due to digitalis. Only one, an internist, remembered any such cases in his experience.

The following cases of digitalis allergy may prove to be of interest.

CASE REPORT

A. B., a 24-year-old female, a nurse, was admitted to the Eagleville Sanatorium March 10, 1939, with a diagnosis of bilateral pulmonary tuberculosis. Past medical history was irrelevant.

The patient denied having had infantile eczema. There was no history of sensitivity to any of the pollens, or of vasomotor rhinitis. Dust in excessive amounts caused paroxysmal attacks of sneezing. There was apparently sensitivity to some forms of sea food, as she often had attacks of urticaria following ingestion of these.

The patient was given 0.5 c.c. of the tincture of digitalis (U.S.P) on the evening of Sept. 30, 1939. Approximately one-half hour later she noted erythema and many hives about the knees. In addition, her face became flushed, and her lips and nose felt swollen. The same phenomenon occurred after 2 further doses (0.5 c.c.) of the medication. The third dose and several successive ones were also followed by nausea and vomiting.

Several additional doses of the tincture of digitalis were given under careful observation to check the patient's reactions. The following findings were observed within from one-half to one hour after the taking of each.

The areas most severely affected were the anterior and medial aspects of the lower third of the thighs and the knees. The skin was definitely reddened and

From the Eagleville Sanatorium.

hot to touch. Many urticarial wheals were scattered throughout these areas. In addition, on several occasions angioneurotic edema of the face was present, plus scattered urticarial lesions over the entire body. The administration of the tincture of digitalis was stopped, and the patient had no further allergic manifestations. Comparable doses of the tincture of digitalis from the same bottle were given to a number of other patients, in order to rule out the factor of possible deterioration products causing the unusual symptoms. These tests were all negative. As a further check, the patient was then given several doses of 0.1 Gm. of powdered digitalis (U.S.P.). Typical allergic reactions, such as those described above, occurred after each dose. She exhibited marked dermographia at the time of taking digitalis. This was much less at other times.

Typical allergic reactions also followed therapeutic doses of digilanid and urginin given by mouth.

Patch tests with the tincture of digitalis and the powdered leaf were negative. An extract of the powdered digitalis leaf was made by Coca's method.[9] The resulting intradermal test was negative.

COMMENT

This is apparently a true case of allergy to digitalis. The patient exhibited the cardinal symptoms of an allergic drug response, i.e., fever, pruritus, urticaria, joint involvement, and edema of the face. (The latter is mentioned by Tuft[10] as having been previously reported in digitalis allergy.) Symptoms occurred only after the ingestion of the drug and were of short duration. During the days when the patient received no digitalis, there were no allergic manifestations. No other medication was taken during this period. When the digitalis was again administered the same symptoms reappeared. Since final cessation of digitalis administration, there have been no further allergic manifestations.

The negative skin tests obtained in this case are compatible with the diagnosis of digitalis allergy, since negative reactions are usually obtained in cases of drug allergy. The latter diagnosis depends largely upon the history, objective findings, and the results of the administration and withdrawal of the suspected agent. It is worthy of note that, following the first dose of digitalis, allergic manifestations appeared within thirty minutes. It is evident that the patient already had an allergy to digitalis, either natural or acquired. Although she had never taken digitalis in the past, she had handled it in her nursing work. The possibility of allergy acquired in this manner should be considered.

The patient's tuberculosis was well controlled at the time of the allergic manifestations.

There were no significant changes in the patient's pulse or blood pressure during any of the tests. There was no eosinophilia. This has been reported in rare instances.[11-13]

CONCLUSION

The findings in a case of allergy to digitalis are reported.

REFERENCES

1. Cushny, Arthur R., Edmunds, C. W., and Gunn, J. A.: A Text Book of Pharmacology and Therapeutics, ed. 9, Philadelphia, 1928, Lea & Febiger, p. 439.
2. Bastedo, Walter A.: Materia Medica, Pharmacology, Therapeutics and Prescription Writing, ed. 4, Philadelphia, 1938, W. B. Saunders Co., p. 215.
3. Sollmann, Torald: A Manual of Pharmacology, ed. 5, Philadelphia, 1936, W. B. Saunders Co., p. 505.
4. Luten, Drew: The Clinical Use of Digitalis, Springfield, Ill., 1936, Charles C. Thomas, p. 72.
5. Coca, Arthur F.: Asthma and Hay Fever in Theory and Practice, Springfield, Ill., 1931, Charles C. Thomas.
6. Heydner, F.: München. med Wchnschr. **58:** 1511, 1911.
7. Urbach, Erich: Klinik und Therapie der Allergischen Krankheiten, Vienna, 1934, Wilhelm Mandrich.
8. Brandt, Robert: Wien. klin. Wchnschr. **50:** 1525, 1937.
9. Coca, Arthur F.: Asthma and Hay Fever in Theory and Practice, 1931, p. 93.
10. Tuft, Louis: Clinical Allergy, Philadelphia, 1937, W. B. Saunders Co., p. 149.
11. Recht, Georg: Wien. klin. Wchnschr. **36:** 415, 1923.
12. Romano, J., and Geiger, A. J.: Am. Heart J. **11:** 742, 1936.
13. Smith, A. E., and Benner, S. R.: Am. Heart J. **7:** 182, 1931.

Annual Review

ALLERGY TO INSULIN, LIVER, PITUITARY, PANCREAS, ESTROGENS, ENZYMES, AND SIMILAR SUBSTANCES

MAX HARTEN, M.D., AND MATTHEW WALZER, M.D.
BROOKLYN, N. Y.

THE rapidly growing number of reports dealing with the untoward reactions which have followed the administration of various hormones, enzymes, and organ extracts has attracted the attention of the immunologist as well as that of the clinician. In view of the urgency which frequently dictates the therapeutic use of such life-saving preparations as insulin, liver, pituitary extract, etc., the importance of being able to distinguish between allergic and nonspecific reactions to these substances is obvious. A search of the literature for information on the immunologic aspects of these questions has been disappointing. Many reports fail to include some of the most elementary facts needed for an immunologic analysis of these reactions. The reviewers have attempted, therefore, to collect the available information on hypersensitiveness to hormones, enzymes, and organ extracts. Although the literature was reviewed carefully, some reports have undoubtedly been overlooked. Others were omitted because they were too incomplete for evaluation. It is to be hoped that this attempt at a summary of the problems involved in these types of allergy will stimulate further investigations to close the large gaps which exist in the knowledge of this subject.

INSULIN ALLERGY

Insulin, the internal secretion of the pancreas, is found in the islet tissue of that organ, and from there it passes into the general circulation. Banting and Best, in 1922, first succeeded in obtaining physiologically active preparations of insulin from the pancreas.

The commercial insulin preparations now available in this country are obtained from beef and hog pancreas. Most preparations are mixtures of insulins derived from both of these sources. Special insulins prepared from either animal are also available.

Jensen[1] has reviewed in detail the various methods employed in the preparation of insulin. Practically all of the procedures are based on the extraction of the minced pancreas with acidulated or alkaline solutions of water, acetone, methyl alcohol, or ethyl alcohol. Purification is achieved by various procedures such as fractional precipitation with alcohol or salts, isoelectric precipitation, adsorption, etc.

From the Allergy Division of the Jewish Hospital of Brooklyn, Brooklyn, N. Y.

In 1926, insulin was isolated in crystalline form by Abel and his coworkers.[2] They found that the chemical reactions of crystalline insulin were those of typical proteins. There is every indication that this crystalline protein represents the complete hormone.[1] The molecular weight of crystalline insulin has been estimated to be from 20,000 to 50,000. The isoelectric point ranges between 5.3 and 5.35.

Crystalline insulins derived from different sources, such as ox, sheep, hog, and fish, are similar in microscopic appearance, isoelectric point, solubility, and in carbon, hydrogen, nitrogen, and sulfur content.[1b, 3] The physiologic action of a unit of crystalline insulin prepared by any of the standard methods of manufacture is almost the same in all insulins regardless of source.[1d]

Early preparations of insulin, derived from either pork or beef pancreas, after purification and recrystallization contained an average of from 0.006 to 0.01 mg. of nitrogen per unit.[2b, 2c, 4] This amount, Tuft[19] believed, was so small that it reduced the probability of inducing hypersensitiveness even on repeated administration. Vaughan[5] points out, however, that the 0.001 mg. of nitrogen contained in one unit of insulin, prepared by the most modern methods, is sufficient to be of allergenic significance. The common forms of insulin, prepared by the new methods now being employed commercially, are said to have a nitrogen content "practically the same" as that of crystalline preparations.[6]

Modified forms of insulin, such as zinc insulinate and protamine insulin,[7] are now being used for the purpose of obtaining slower and more prolonged absorption. The protamines are derived from the sperm of various fishes, e.g., salmine from salmon. They are sulfur-free compounds, rich in nitrogen and of high molecular weight.[8, 9] Kern[8] has recently investigated the antigenicity of protamine in guinea pigs. Four animals were injected intraperitoneally with 1 c.c. of salmine at three-day intervals for three doses and were tested intravenously two weeks later with 0.5 c.c. No symptoms of anaphylaxis were noted. This seems to confirm the observations of previous workers[9,10] that the protamines lack antigenic properties. The protamine fraction may therefore be excluded as an etiological factor in cases of allergy to protamine insulin.

The Antigenic Properties of Insulin in Animals.—In view of the prevalence of insulin sensitivity in human beings today, there is a surprising paucity of experimental work dealing with the antigenic properties of insulin in animals. The difficulties encountered in such investigations because of the physiologic action of the antigen may explain to some extent the meagerness of the studies on this subject.

Only a few workers have studied *complement fixation* with insulin in animals. In 1926, Ornstein and Mera[11] injected rabbits with commercial insulin and with an insulin-hog-serum mixture. Complement-fixing antibodies could not be detected in the blood of these animals.

Positive results, however, were obtained in the recent experiments of Wasserman and his co-workers.[12] They injected rabbits with commercial beef or pork insulin. Almost daily intravenous injections were given for a period of three weeks or longer. Tests for complement fixation were made with the commercial or crystalline forms of the heterologous insulin. In this manner, it was possible to eliminate reactions which might be due to species protein rather than to the insulin itself. Complement-fixing antibodies were definitely demonstrated in six of eleven animals. The absorption of species protein antibody with an excess of animal protein did not influence the complement fixation reaction with insulin.

Precipitin studies in animals, made in an effort to demonstrate the antigenicity of insulin, have been inconclusive. In the above-mentioned experiments of Ornstein and Mera,[11] it was found that normal human, guinea pig, beef, hog, and horse sera in dilutions of 1:100 gave positive ring tests with a 1:5 dilution of insulin. The authors concluded that animal and human sera precipitate insulin nonspecifically. Wasserman,[12] in the above-mentioned studies on complement fixation in rabbits, and Bernstein,[13] in anaphylactic studies in guinea pigs, both reported inconclusive findings in their efforts to demonstrate precipitin antibodies to insulin. Clutton, Harrington, and Yuill[14] failed to demonstrate precipitins to insulin even when it was coupled with o-b-glucosidotyrosol, although indirect evidence is submitted that the combination is antigenic. In the anaphylactic experiments which are to be mentioned below, precipitin studies were not reported.

Anaphylactic experiments in guinea pigs, with insulin as an antigen, were first reported by Duenner and Dohrn[15] in 1928. Definite evidence of anaphylaxis was obtained in animals sensitized with commercial insulin. In some of these animals, however, anaphylactic reactions could be obtained also with the protein of the animal from which the insulin was derived. Since there was sufficient species protein in the insulin to induce sensitization, the results obtained cannot be considered conclusive evidence of the antigenicity of the insulin itself.

In 1931, Cade, Barral, and Roux[16a] published experiments which were more convincing. They sensitized guinea pigs with commercial insulin and produced anaphylactic reactions with the same substance. Guinea pigs, injected with the serum from dogs sensitized with beef insulin, could be shocked with this insulin but not with beef muscle or beef pancreas. In another series of experiments,[16b] guinea pigs sensitized with beef serum or pancreas developed no anaphylactic reactions when tested with a beef insulin. Four of eleven animals sensitized with this beef insulin developed typical anaphylaxis when tested with the same preparation. Negative results were obtained when animals actively sensitized with beef insulin were tested with beef serum or beef pancreas. The authors concluded that insulin was antigenic and that it lacked organ- and species-specific factors.

Several recent experiments have confirmed the findings of these earlier workers. Lewis,[17] in 1937, employed the Schultz-Dale technique to study the antigenic properties of insulin. Uterine strips of guinea pigs sensitized with beef or pork insulin were tested with the homologous or heterologous insulin and with beef pancreas and serum. Although the insulins employed were not crystalline, they were described as "almost as pure as crystalline insulin." In the uterine strips of animals sensitized to beef insulin, specific contractions could not be induced with beef pancreas or serum. Positive results, however, were obtained with beef insulin, indicating that this product contained little or no species antigen. The uteri of animals sensitized with either the beef or pork insulin responded to tests with the heterologous insulin. Following complete desensitization with the heterologous insulin, the addition of homologous insulin to the bath usually elicited another specific contraction, indicating the presence of specific as well as common antigens in both the insulin preparations. Hence, Lewis concluded that insulins from different sources are closely related, but are not completely identical. He believes that there is a residuum of specificity in insulin which is inherent to the species but which differs from the other proteins of the same species.

The most recent experiments in guinea pigs were reported by Bernstein, Kirsner, and Turner[13] in 1938. As antigens, they employed a common brand of insulin (beef and pork), a highly purified preparation (beef), and crystalline insulin. The strongest anaphylactogenic properties were found in the crystalline insulin.

In several of the above sensitization experiments, attempts were made to enhance the antigenicity of the insulin. Wasserman[12] tried horse serum as a synergistic antigen and pilocarpine as a parasympathetic stimulant, with indifferent results. Bernstein,[13] using horse serum as a synergistic antigen, found some enhancement of sensitivity when the animals were tested at the end of three weeks. At six weeks, however, the anaphylactic reactions were no stronger in these animals than in those sensitized with the insulin alone. At this time, reactions of greater severity were obtained than at the previous testing. The intravenous method of sensitization showed no advantage over the subcutaneous route in the production of sensitivity to insulin.

Antigenic Properties of Insulin in Human Beings.—Reports on hypersensitiveness to insulin in human beings are much more numerous than those dealing with hypersensitiveness in animals.

The search for *precipitin antibodies* to insulin in human serum was handicapped by the same difficulty which Ornstein and Mera[11] had encountered in animal investigations: namely, practically all sera, including those from human beings, form precipitates with insulin. Hence, the earlier reports[18] of the presence of precipitins to insulin in human sera are subject to question. In 1928, however, Tuft,[19] by a special

technique, succeeded in demonstrating the presence of precipitins to insulin in a human serum. He employed purified crystalline insulin and a capillary tube technique to obviate the factor of nonspecific precipitation. He found precipitins in a titer of 1:3,000 in the serum of a patient sensitive to insulin, as compared to a titration of 1:100 in normal control sera. This patient had previously received insulin, without any untoward reaction. Following an interval of one year, insulin treatment was renewed. Urticaria, nausea, and weakness developed ten days after the resumption of treatment. A subsequent search for precipitins in this patient after an interval of five weeks yielded negative findings.

Since Tuft's investigation, Karr and his co-workers[20] reported the presence of precipitins in the blood of a patient who developed severe indurated reactions at the sites of the insulin injections. The details of the technique were not reported. In another report by Fiandaca,[21] the serum was tested for precipitins, but none were detected. With an original technique involving the combined methods of agglutination of insulin-coated collodion particles and the resuspension-agglutination technique, Cannon and Marshall[22] recently demonstrated precipitins in the sera of several patients hypersensitive to insulin.

Tuft,[19] and also Raynaud and Lacroix,[18] who reported positive precipitin findings, investigated the sensitizing power of their precipitin-bearing sera in guinea pigs. The results obtained in the two investigations were contradictory. In neither case, however, were sufficient animals used to render the results convincing. Tuft[19] injected one guinea pig with 3 c.c. of serum from his insulin-sensitive patient and obtained no anaphylactic symptoms when the animal was tested intravenously with 0.1 c.c. of insulin. In the investigations of Raynaud and Lacroix,[18] in which positive results were reported, the technique employed and the conclusions drawn are subject to question.

Considerable work is still needed to indicate the conditions which favor the induction of precipitin antibodies. The wider application of the more refined techniques of Cannon and Tuft is needed to yield further information on this aspect of insulin hypersensitiveness.

It is of interest to note in passing that in two patients in whom precipitins were reported,[19, 20] skin-sensitizing antibodies (reagins) were also found.

A search for *complement-fixing antibodies* in the cases reported by Tuft[19] and Fiandaca[21] yielded negative findings. The significance of this particular type of investigation, however, is questionable in view of the recent studies of Richardson,[23] who found many human sera with the power of fixing complement in the presence of insulin. This occurred among patients with thyroid disease, pregnancy, diabetes, and other illnesses, as well as among normal persons. The blood Wassermann reactions in most of these cases were negative, and when positive,

they bore no relation to the complement-fixing power of the serum with insulin. The antigens used in these experiments were pork, beef, and crystalline insulins. The nature of this complement-fixing reaction in connection with insulin has not yet been defined.

The presence of *skin-sensitizing antibodies (reagins)* was investigated in only nineteen of the 200 reported cases of insulin allergy.

As in cutaneous testing, it is difficult to interpret the results obtained in the passive transfer studies of some workers because the details of the technique employed in the investigations were not reported. Some even failed to mention the nature of the insulin preparations which were used in testing the passively sensitized sites. Some impaired the value of their investigations by using as much as 0.1 c.c. of antigen for testing the passively sensitized sites. Nevertheless, the evidence is conclusive that skin-sensitizing antibodies may be present in some forms of insulin allergy in which positive cutaneous reactions to insulin are demonstrable. The early impression by Fiandaca[21] that only those patients have reagins who manifest three- or four-plus cutaneous reactions to insulin has not been borne out by subsequent investigations. The presence of reagins bears no direct correlation to the degree of the cutaneous reaction.

Among the nineteen reported passive transfer studies, nine were not made with crystalline insulin, and the results, therefore, are not conclusive. Of the ten patients tested with crystalline insulin, eight showed the presence of skin-sensitizing antibodies. These eight gave negative reactions to beef and pork proteins on direct testing.

In four of these eight patients skin-sensitizing antibodies were sought and found during the first course of insulin treatment.[24, 28-30] In the remaining four they were detected in the second course.[19, 27, 29, 31] The possibility cannot be excluded that reagins may have been present already in these four patients during the first course of treatment, since, in three of them, marked local reactions were already noted during the first series of injections.[19, 29, 31] On the other hand, marked local reactions cannot be considered as pathognomonic of the presence of reagins, for in two patients in whom no reagins were found, marked local reactions were also reported.[19, 26] It is of interest to note at this point that reagins may be present in cases of insulin allergy in which the primary manifestation is a marked local reaction unaccompanied by any general symptoms.

No information is as yet available as to the time needed for the production of reagins following the first administration of insulin or during the first course of treatment. During a second course of therapy following an insulin-free interval,[19] reagins have been detected after six or seven weeks.

In regard to their persistence in the circulation, reagins to insulin were still present in Tuft's case[19] five weeks after their presence was

first noted, but had disappeared before a subsequent examination was made about two months later. In Bryce's[31] patient reagins were still present three months after they were first found. Tuft[19] also brought out the fact that in his case reagins persisted after the precipitin antibodies had disappeared.

As in other forms of reaginic sensitivity, cutaneous hypersensitiveness may outlast the presence of reagins in the circulation.[19, 31]

Data on the atopic status of the cases reported are lacking in most instances. Of the 8 patients in whom reagins to crystalline insulin were found, only two were reported to be atopic.[30, 31] One of these two patients was not diabetic.[30] Of the remaining six, five were diabetic.[28]

Skin-sensitizing antibodies have been demonstrated for various commercial insulins, crystalline insulin, animal proteins, pancreatic tissue extracts, pancreatic enzymes, etc. This question will be discussed under "Cutaneous Testing."

Incidence.—Of approximately 200 cases of insulin allergy, forty-two were reported during the early years of insulin treatment (1922 to 1930). Antonini[33] has reviewed the cases reported up to 1925, and Cade,[16a] those up to 1931. Since 1931, 153 cases of insulin allergy have been reported. The incidence of allergic reactions to insulin varies widely in the reports of different workers. Some consider even the slightest local reactions as allergic manifestations. Others excluded all local reactions regardless of severity and designated as allergic only those patients in whom insulin therapy had to be discontinued. Hence, we have such wide variations in reported incidence as: Hallerman,[95] 2 per cent; Umber,[94] 2 per cent; Allan and Scherer,[32] 11.7 per cent (for 1931 series); Collens,[72] 7.3 per cent; von Grafe,[69] 0.15 per cent; Murphy,[34] 0.2 per cent. (For more detailed information on this aspect of the subject, the reader is referred to the review by Herzstein and Pollack.[36]) Local reactions,[37] as well as general reactions consisting for the most part of generalized urticaria, have also been reported for protamine zinc insulin.[5, 8, 37, 38]

Only nine[6, 25, 30, 35, 52, 95] of the 200 cases of insulin allergy which were reviewed occurred in nondiabetic patients. These were usually found in patients being treated with insulin because of malnutrition. In his series of 100 malnutrition cases, Blotner[35] found only three instances of insulin allergy. Ulrich, Hooker, and Smith[51] suggest that the incidence of allergic reactions may possibly be higher among nondiabetic than among diabetic patients. Until definite criteria for allergic reactions are adopted, this question cannot be answered.

Despite the present high degree of purity in commercial insulin preparations, an increasing number of cases of insulin allergy are finding their way into the literature. In view of the widespread use of insulin, however, the incidence of insulin allergy must still be considered low.

Among the forty reported cases of insulin allergy in which data concerning the age of the patient were available, there were three patients in the first decade,[39-41] one in the second, eight in the third, ten in the fourth, eleven in the fifth, six in the sixth, and one in the seventh.[29] The majority of cases seemed to occur between the ages of 31 and 60, the period in which diabetes mellitus most frequently occurs.

Statistics on the sex of the patients with insulin allergy were available in only fifty-seven of the reported cases. Of these, forty-seven were females and ten were males. All cases reported were of the white race.

Incidence in Atopic Persons.—Of 195 cases reviewed, there were only thirteen (6.7 per cent)[26, 30, 32, 34, 42, 47] who were definitely designated by the authors as atopic. The theoretic significance of this question was probably unrecognized by a majority of the authors, as most of them made no mention of this point in the histories of their patients.

Although diabetes mellitus and atopy may coexist, there appear to be few instances of the occurrence of diabetes in allergic patients.[13] Joslin,[48a] in 1928, recorded only six cases in which both conditions occurred simultaneously. Swern,[49] reviewing the case reports of 4,000 allergic patients, found only six who also had clinically evident diabetes. Kern,[50] in a preliminary search, found only one diabetic patient among 1,600 patients with hay fever and asthma, and this patient proved to be the only asthmatic person among 1,400 diabetic persons. After a more thorough investigation of the subject, Kern found that, although diabetes mellitus and allergy (atopy) rarely occur simultaneously in the same patient, there is a relatively high incidence of positive histories of allergy among diabetic patients. There were sixty-one positive histories of allergy among 300 diabetic patients, an incidence of 20.3 per cent, which is a higher percentage than occurs in the community at large. In forty-six of these sixty-one cases, the allergy had ceased before the onset of the diabetes. In five, the allergy disappeared shortly after the diabetes started. In nine instances, both conditions were present. Kern also reported that among 500 allergic patients, 21 per cent gave a positive family history of diabetes and 18.4 per cent a positive history of both diabetes and allergy. Hence, although positive family and past histories of these two conditions are frequently obtained in the same person, the two illnesses are rarely coincident.

Incidence During the First Course of Treatment.—In only fifty of the reported cases of insulin allergy was there any definite information given as to the exact time of onset of the allergic symptoms.

Some of these reactions occurred during the first course of treatment. In a number of these cases, severe local[53, 54, 95] and general[55-57] reactions were reported following the first injection of insulin. A positive history of atopy was obtained in only two of these patients.[26, 43] Most of the reactions occurred from three to fourteen days after the onset of treatment.[16a, 32, 59, 60] In occasional instances, however, they failed to de-

velop until insulin treatment had been under way for from one[26] to ten[39] months. With protamine insulin reactions were noted as early as the tenth day.[38]

Incidence During the Second Course of Treatment.—In many instances, insulin allergy did not develop until after an interruption in treatment. The insulin-free interval between the first and second courses varied from ten days[62] to seven years.[46] The duration of the insulin-free period had no noticeable effect on the nature, severity, or time of onset of the subsequent allergic reaction. On occasions, it followed the first injection of the second series;[45, 62-64] in other cases, it occurred from four[32, 65] to fourteen days after the treatment was renewed. This "latent period" seemed to resemble that commonly observed in the first course of insulin therapy. The similarity of this "latent period" to the "incubation period" of almost similar duration which characterizes serum sickness has been noted by many of the authors.

It is interesting to note that in all the cases in which allergic manifestations occurred during a second course of treatment following an insulin-free period, these reactions were of the generalized type. A large number of these patients had, however, experienced mild[19, 66, 67, 96] or severe[31, 63, 68] local reactions during the first course of treatment.

Infection has been reported to have been a factor contributing to the onset of insulin allergy in some instances.[49, 90-92] As such reports are few, it is not unlikely that the infections were purely coincidental in these cases.

Symptomatology.—There are three types of reactions to insulin: (1) mild local reactions at the site of injection; (2) severe local reactions; (3) general reactions.

The *mild local reactions* at the site of injection usually consist of erythema[69] or slight local induration which tends to disappear in from one to three days.[32] These reactions are probably nonimmunologic in nature and are of little clinical significance.[19]

The *severe local reactions* which occur at the site of injection usually consist of erythema and local edema measuring up to 10 cm. or more in diameter. They may be accompanied by pruritus, and their induration may develop to such a marked degree as to require incision.[16a, 39, 63, 70] These reactions may be immediate, occurring within an hour after the insulin injection,[29] or they may be delayed for from six hours to several days[56] after the injection. According to Laurence,[71] the delayed local reactions are usually much more intense than the immediate ones. Collens[72] reported thirty instances of local reactions in 407 insulin-treated patients. In only five of these patients were the reactions so marked as to necessitate discontinuance of the insulin treatment.

In contrast to the deep-seated edematous reactions, superficial urticarias, localized to the site of injection, have also been reported. Three

of the patients with this symptom were atopic.[30, 44, 46] Another patient with this type of reaction proved to be sensitive to pork protein and not to insulin.[6]

Sixty-three cases in which *general reactions* occurred have been reviewed. The general reactions have been of several types. The most common manifestation was generalized urticaria[73-77] which, at times, was preceded by localized urticaria at the site of injection.[30, 46, 78] This urticaria was frequently associated with angioneurotic edema involving the face,[55, 79, 80, 81] glottis and tongue,[27, 36, 82] genitals,[67] or other parts of the body.[58] Edema of the throat may have been responsible for some instances of difficulty in breathing which was not asthmatic in nature. Generalized erythemas,[83] pruritus without urticaria,[36] and eruptions of a morbilliform,[16, 84] scarlatiniform,[84] or vesicular type[84] have also been reported. In many instances,[31, 32, 56, 85] immediate severe local reactions at the injection sites have preceded the onset of generalized symptoms.

Symptoms of circulatory failure, e.g., collapse,[75] tachycardia,[29, 52] weakness,[29, 45] and vertigo,[21] have occurred singly or in association with generalized urticaria and angioneurotic edema.[64, 81] Bronchial asthma[31, 34] has also been reported as a lone symptom or accompanied by generalized urticaria[45] or nasal symptoms.[44, 45] Marked constriction of the chest associated with generalized urticaria and fall in blood pressure has been noted.[51] In another case, spontaneous abortion and pulmonary edema, together with generalized urticaria, were described.[24] Gastrointestinal symptoms such as nausea,[64, 81] vomiting, severe pylorospasm,[86] diarrhea, and abdominal cramps[87] have also been encountered.

Since the introduction in 1936 of protamine insulin, reactions of various types following the use of this product have also been reported. As in the case of plain insulin, these have included slight local reactions,[88] severe local reactions,[8] generalized urticaria,[5, 37, 38] and angioneurotic edema.[42] Kern[8] reported a case with purpura following the use of both regular and protamine insulins. Bronchial asthma, together with generalized urticaria and angioneurotic edema, was observed by Herold[42] in an asthmatic patient under protamine insulin treatment for diabetes.

No fatal immediate reactions following the use of insulin have been reported. However, several deaths have been attributed indirectly to insulin allergy.[83, 89, 90]

The resemblance of some of the insulin reactions to serum sickness has been pointed out by many observers.[19, 33, 66, 72] In both types of conditions erythemas,[33] fever,[52, 67, 71, 83] joint symptoms,[44, 60] urticaria, and generalized edema have been noted. Their similarity to serum sickness with regard to the "latent period" has already been mentioned.

Cutaneous Testing.—Cutaneous testing with various insulin preparations has been reported in thirty-five cases. A critical analysis of the

results obtained is difficult because of the absence of information on technical details in some reports and because of the questionable testing procedures employed in others. Some workers have injected as much as from 0.05 to 0.2 c.c. of extract in performing intracutaneous tests. The introduction of such large amounts of allergen not only results in false positive reactions but, as will be noted below, also increases the incidence of constitutional reactions. Regardless of the dilution of the material employed, no more than 0.02 c.c. of extract should be employed in intracutaneous testing.

Positive reactions in cases of insulin allergy have been obtained by some workers with scratch tests in which undiluted preparations of sheep, beef, pork, and horse insulin were employed.[18, 65] In one instance, a positive scratch reaction was elicited with a 1:10 dilution of a highly purified insulin preparation, but a negative reaction resulted upon further dilution of the extract.[43] Positive results with the intracutaneous technique have been reported in some instances in which the scratch method elicited only negative reactions.[34, 66] In some cases, it was possible to elicit positive reactions by the intracutaneous technique with 1:100 dilutions of the insulin preparation.[74] It was observed generally that the degree of the cutaneous reaction was proportional to the unit concentration of the insulin extract which was employed.[19, 63]

It is unfortunate that many workers who reported positive cutaneous reactions to various insulin preparations did not test with crystalline insulin. A positive reaction to crystalline insulin would be weighty evidence in favor of true insulin sensitivity, whereas a negative reaction, according to Tuft,[19] would virtually exclude the presence of such an allergy.

Many patients who reacted to insulin obtained from various animal sources as well as to crystalline insulin showed negative skin reactions to beef,[28, 29, 31] pork,[19, 24, 51] sheep,[36, 68] and horse[63] proteins. Such patients manifest a true sensitivity to insulin which is not based upon a species-specific factor. Further evidence of this fact is found in the case reported by Campbell[24] in which positive reactions were obtained with fish and human insulin preparations, as well as with pork, sheep, beef, and crystalline insulins.

In a series of cases tested by Campbell,[24] the reactions obtained with crystalline insulin were, as a rule, weaker than those elicited with other insulin preparations. A similar result was obtained by Hansen,[63] but the findings of other investigators[19, 34, 68, 74] did not confirm this observation.

It is a common clinical observation that patients who react unfavorably to insulin from one source may be able to tolerate insulin derived from another animal. It is generally assumed that in such cases the sensitivity is to the animal protein rather than to the insulin principle

itself. Unfortunately, most of the information on this question is derived from clinical trials and not from cutaneous testing. Cohen and Simon,[6] however, have reported a clear-cut case in which cutaneous tests definitely established this point. This patient, who gave negative personal and family histories of atopy, developed severe local reactions following insulin injections. Negative cutaneous reactions were obtained to tests with beef insulin and crystalline insulin, but positive reactions were obtained to pork insulin and to pork protein. In this instance, the allergic reaction was undoubtedly elicited by the protein source of the insulin and not by the pure insulin principle.

There is as yet no case on record in which coexisting sensitivities to both the insulin principle and the animal source have been demonstrated.

The relation between sensitivity to insulin and sensitivity to pancreas and deinsulinized pancreatic tissue has also been investigated. The reports on this subject by Cade, Barral, and Roux[16] and by Lewis[17] have already been presented (see "Antigenic Property of Insulin in Animals"). They showed by sensitization experiments in guinea pigs that no demonstrable common antigen exists in the pancreas and in insulin from the same animal. These findings were borne out in human studies on a patient described by Battistini,[28] who showed positive reactions by direct and transfer tests with commercial and crystalline insulins, but who gave negative reactions by direct and transfer tests with deinsulinized pork pancreas. In the case reported by Tuft,[19] positive direct and transfer tests were obtained with commercial and crystalline insulins and also with beef and pork pancreatic extracts. The report does not state whether deinsulinized pancreas was used in the preparation of the pancreatic extract. It is unfortunate that no skin tests with insulin were reported in Criep's[93] cases, in which sensitivity to deinsulinized pancreatic tissue was definitely demonstrated. While the data on the relationship of insulin hypersensitiveness to pancreatic tissue allergy are still too meager to permit final conclusions to be drawn at this time, the evidence seems to point to an absence of organ specificity in hypersensitiveness to crystalline insulin.

In analyzing the possible antigens which may be involved in allergic reactions following the injection of insulin, it is well to keep in mind the case reported by Cohen and Simon.[6] This patient gave positive reactions to commercial insulin preparations but not to crystalline insulin. Further study seemed to implicate amylopsin as the offending factor. This case will be discussed in greater detail later.

It has already been brought out that many of the positive cutaneous reactions to crystalline insulin are mediated by the reagin, the presence of which can be demonstrated by the passive transfer technique. Another aspect of this question is presented in the recent case report of Ulrich, Hooker, and Smith.[51] Their patient was a 53-year-old non-

diabetic patient with a doubtful atopic history, who developed a generalized urticaria a few days after the beginning of a second course of insulin therapy. Subsequent injections produced constriction in the chest, urticaria, chills, and a drop in blood pressure. Positive cutaneous reactions and constitutional symptoms followed intracutaneous tests with crystalline insulin. Negative reactions were obtained with pork and beef protein. The positive reaction to crystalline insulin could not be transferred passively to normal skin. This demonstrated that, in some forms of insulin allergy, as well as in other types of acquired sensitivity, specific cutaneous reactions may occur in the absence of reagins. That more than one allergic mechanism may be involved in acquired sensitivities to a single antigen has already been observed in connection with other antigens of animal origin (horse serum, *Ascaris*, etc.).

Little effort has been made to study the duration of cutaneous sensitivity to insulin. The impression obtained from scattered reports is that this form of allergy, like other types of induced sensitivity, is transitory. Corcoran,[46] whose patient showed positive cutaneous reactions to crystalline insulin, obtained positive reactions upon retesting after an interval of one year. Retests at the end of the second year, however, proved to be negative. It has already been pointed out that skin-sensitizing antibodies to insulin tend to disappear from the circulation within a few months.[19]

Positive cutaneous reactions to crystalline insulin may be commonly elicited in patients in whom severe local reactions following the injection are the only manifestation of the allergic reaction.[24, 28, 29] They may also be elicited in patients in whom little or no local reaction follows the injection of insulin, but in whom a general reaction is the expression of the allergy to insulin.[19, 30] The relationship of reagins to both of these types of reactions has already been discussed.

Care should be exercised in the cutaneous testing of patients with insulin allergy because constitutional reactions have resulted from the intracutaneous injection of minute amounts of insulin.[27, 75, 80] A general reaction was induced in one instance by the intracutaneous injection of 1/20,000 unit,[31] and in another case by a test with 0.1 c.c. of a 1:1,000,000 dilution of insulin.[43] Intracutaneous tests with crystalline insulin[42, 66, 79] have been responsible for general reactions in some cases. In one instance, the application of a patch test with insulin resulted in a severe general reaction.[27]

A search for reagins for insulin was made in only two of the patients with constitutional reactions. It is noteworthy that these antibodies were found to be present in both instances.[27, 31]

The symptoms of a constitutional reaction resulting from a skin test with insulin usually simulated the allergic reaction which followed the

therapeutic injection. The skin test usually produced a marked reaction, with pseudopodia.[31, 42] The most common constitutional symptoms were urticaria and angioneurotic edema. In two patients who were atopic, asthmatic symptoms were a part of the reactions,[31, 42] which also included lacrimation, cyanosis, and nausea. These reactions responded to the administration of epinephrine. In the light of the above experiences, Sammis[30] advised that intracutaneous skin tests with insulin be performed with extreme caution, particularly in atopic persons.

Intracutaneous tests with insulin resulting in marked cutaneous reactions may increase temporarily the permeability of the tested sites. This was borne out by the experience of Schill,[67] who reported the flare-up of a site previously tested with 0.2 c.c. of a 1:10,000 dilution of crystalline insulin, upon the intracutaneous administration of a desensitizing dose. In another instance reported by Lasch,[27] cutaneous sites tested four days previously flared up following the oral administration of 3 c.c. of insulin. Following this symptom, the patient experienced diarrhea, urticaria, and angioneurotic edema. This report takes on additional significance in that it demonstrates the passage of orally administered insulin into the bloodstream in amounts sufficient to induce a constitutional reaction.

Positive cutaneous reactions to insulin are uncommon in the general population. Tuft[19] obtained negative reactions in ten diabetic and twenty normal persons who were tested with commercial and crystalline insulin preparations. Allan and Scherer[32] noted only occasional reactions in diabetic patients. Sammis[30] tested eleven hay fever patients with insulin. Only one subject gave moderate reactions to two of three insulin preparations; the others showed negative or negligible reactions. Herzog[29] reported a high incidence of positive reactions in a series of 50 normal adults. His study, however, is subject to criticism in that his tests were performed with 0.1 c.c. of extract on the backs of his patients, a technique which favors the production of nonspecific reactions.

Kern[8] performed intracutaneous tests with 0.02 c.c. (0.1 mg. N per c.c.) of protamine (salmine) solution on 100 control subjects and 104 diabetic persons, who were receiving protamine insulin. No positive reactions were obtained in any of these patients, although seventeen of them had experienced marked local edematous reactions following therapeutic injections of protamine insulin. In another study on eight atopic patients who showed positive cutaneous reactions to salmon, negative reactions to salmine were obtained. All reports seem to indicate that positive cutaneous reactions to protamine insulin are always associated with positive cutaneous reactions to other insulins, such as beef, pork, and crystalline insulin.[8, 36, 38] One may conclude, therefore, that cutaneous tests with protamine insulin have the same specific significance as tests with other insulin preparations.

Insulin Refractoriness and Its Relation to Insulin Allergy.—There have been a number of cases reported in which the appearance of allergic reactions to insulin (i.e., urticaria and marked local reactions) were said to coincide with a sudden lack of response to insulin treatment.[46, 61, 76, 77]

Glassberg, Somogyi, and Taussig[47] described the case of an atopic person with diabetes, who was resistant to insulin treatment and required 300 units of insulin daily. Injections of insulin from various animal sources resulted in severe local reactions. Gradual desensitization with insulin was followed by gradual diminution in the insulin refractoriness. In a case reported by Karr and his co-workers,[20] the development of extensive indurated local reactions following insulin injections was accompanied by severe insulin refractoriness. Following improvement of the insulin allergy, the insulin requirements were reduced markedly. Williams[86a] described the case of a diabetic child who experienced severe gastrointestinal disturbance following subcutaneous administration of pork insulin. This was associated with an increasing acidosis and refractoriness to insulin. A change to beef insulin resulted in rapid cessation of the allergic symptoms and insulin refractoriness. Data on cutaneous testing were not available in this case.

Insulin refractoriness is by no means a constant accompaniment of insulin allergy. Several observers have been unable to detect any change in the physiologic action of insulin in their cases of insulin allergy.[32, 36, 37] These observations are supported by recent animal investigations. Wasserman and his co-workers[12] demonstrated that the antibodies to insulin in sensitized rabbits do not behave as insulin antihormones. They are, therefore, disinclined to support the hypothesis that insulin resistance as it is observed clinically is the result of a specific insulin antihormone. Bernstein and his co-workers[13] are of the same opinion.

An explanation for some of the reported cases of insulin refractoriness may be found in the recent suggestion of Cannon and Marshall[22] "that some instances of insulin resistance in patients hypersensitive to insulin may be due to the greater localizing capacity of the subcutaneous tissues for insulin and a correspondingly slower absorption of the precipitated insulin protein." It is not likely, however, that this hypothesis would apply to all cases of insulin allergy, as it appears probable that more than one immunologic mechanism is involved in the mediation of the different types of insulin reactions. Under the circumstances, it need not be expected that insulin allergy would always be accompanied by insulin refractoriness.

Treatment.—Some of the problems dealing with local reactions following insulin injections have been solved by a more complete knowledge of some of the nonspecific factors which may be involved. Many chemical irritants[19, 32, 89] which were present in the earlier insulin prod-

ucts have now been eliminated by improved methods of extraction and purification. The preservative employed has been found to be a factor in some cases.[94, 96] Attention has been called also to the fact that the incomplete elimination of alcohol used for sterilization of the syringe may cause some difficulty.[8] The possibility that the formalin in the cleansing alcohol may produce a contact dermatitis and local reactions has also been recognized.[48, 68]

Many mild local reactions may be eliminated by injecting the insulin deeply into the subcutaneous tissues so that none gets into the skin.[97] Changing the site of injection has also been found helpful in some cases where the local reaction was not severe.[29, 71]

One of the most effective means of eliminating both local and general reactions is to change the brand of the insulin to one derived from another species or to employ crystalline insulin. The rationale of this practice has already been discussed. There can be no doubt that changes in the preparation employed may overcome a nonspecific etiological factor in some cases, or even a specific factor, such as sensitivity to the animal which is the source of the insulin. It is not likely to succeed in the presence of a true sensitivity to the insulin protein.

Various methods have been recommended for the specific management of insulin sensitivity. They have been used with variable degrees of success. Whether a true "desensitization" is effected by these procedures or whether the result is that of a "hyposensitization" in the sense in which this term is employed in atopic illnesses is not yet clear. In view of the fact that the mechanisms involved in the production of allergic reactions may differ in the various forms of insulin hypersensitiveness, it would be foolhardy to attempt an explanation of the effects produced by specific treatment. Further immunologic studies on the various etiological mechanisms involved are needed before this question can be clarified. The term "desensitization" is employed in this connection, therefore, in its clinical rather than in its immunologic sense.

The initial dose, the rapidity of increase, the interval between doses, and the route of administration varied with the observer and with the nature of the case.

The initial dose in the most common methods of "desensitization" is usually about 1 unit of insulin diluted in 0.5 or 1 c.c. of saline, given subcutaneously. In subsequent doses, increases of 1 or more units are given daily until the required amount of insulin is tolerated. Increases in dosage may be more rapid and the interval between doses may be diminished depending upon the tolerance of the patient and the urgency of the case. The desired end may be obtained in from five days to three months.[43, 65] In very sensitive cases it may be necessary to decrease the initial dose to 0.0001 unit or less, in order to administer an amount which can be tolerated.[27, 72]

More rapid methods of "desensitization" have been employed by some workers.[46, 51] In these cases, the initial doses are smaller than in the slower methods. The increase in dosage is more gradual, but the interval between doses is considerably shorter. In some it may be reduced to fifteen or thirty minutes. Some advise subcutaneous[46] and others intracutaneous[87] administration. A fair tolerance to insulin has been built up in some cases in less than a day.[46]

Untoward reactions which developed in the course of these procedures were controlled by the administration of epinephrine.

As is to be expected from experience with hyposensitization in atopic illnesses, there are many patients with insulin allergy in whom the above procedures are ineffective. In some, the tolerance cannot be increased;[45] in others the beneficial effects are only temporary.[32, 72, 87]

In an evaluation of the above procedures, attention has been called to the fact that the loss of allergy to insulin may occur spontaneously.[32, 53, 54, 56] Hence, not all of the "desensitizations" reported in the literature can be accepted as authentic examples of the direct effects of specific therapy.

Several nonspecific measures have been recommended for the control of severe local reactions following insulin injections. The use of calcium injected with the insulin[57] or prior to it[55, 75, 98] has been suggested. Allan and Scherer,[32] however, did not find it effective. The subcutaneous injection three times weekly of gradually increasing doses of histamine has also been recommended by Collens.[72] Herzstein[36] and Murphy,[34] however, obtained negative results with this procedure in their cases. Recently Roth[99] and Wilder[37] have reported good results in eliminating local reactions in ten of twelve patients within a period of from two to ten days by the daily oral administration of from 45 to 80 units of histaminase. Further reports on this procedure are awaited.

Classification.—The available information on the immunologic mechanisms involved in insulin allergy is too incomplete to justify a classification of the various types of reactions which have been reported. The subject has been complicated by the fact that many of the reports of insulin allergy were probably those of patients sensitive to the protein source rather than to the insulin principle itself. In addition, nonspecific reactions of various types have been mistaken for manifestations of hypersensitiveness. Excluding these reports from consideration and analyzing those phenomena which appear definitely to be allergic reactions to the insulin principle itself, it becomes evident at once that in allergy to insulin, as in allergy to horse serum, more than one immunologic mechanism is involved.

Among the different forms of sensitivity to insulin, it is possible to recognize certain types which resemble those encountered in serum allergy.[100] One type of insulin hypersensitiveness seems to simulate serum sickness in several respects. Resemblances worthy of note are the

absence of an atopic predisposition, the tendency toward a "latent period," the irregular appearance of reagins and precipitins which are not of prolonged duration, the tendency toward local as well as general types of reactions, and the predominance in the symptomatology of urticaria and angioneurotic edema, associated at times with fever, joint symptoms, etc.

Counterparts to the immediate types of allergic reactions to horse serum also appear to be represented among the insulin reactions. For example, there appears to be an acquired type of insulin allergy in which a positive cutaneous reaction is present without skin-sensitizing antibodies in the bloodstream. Other types in which reagins have been found are also encountered. These occur among nonatopic as well as atopic persons. The presence of the atopic shock organs in the atopic patients tends to influence the symptomatology of their allergic reaction.

It is possible that the dissimilarities between serum and insulin allergies may be explained, to a great extent, by differences in the methods and frequency of administration and in dosage, as well as in qualities of the antigens themselves. All of these questions need further elucidation.

Hypersensitiveness which appears to be manifested toward substances concerned in the normal physiology and metabolism of the body naturally involves the problem of isoantigens and isoantibodies. Since no experimental contributions have been made in this field in relation to insulin, a discussion of the purely hypothetical aspects of the question does not seem advisable at this time.

ALLERGY TO LIVER EXTRACT

The therapeutic use of liver in pernicious anemia, a procedure introduced by Minot and Murphy[101] in 1926, inaugurated a new era in the treatment of anemias. Liver preparations were given orally until the parenteral method of administration was successfully introduced by Gaensslen[102] in 1933.

Liver extracts derived from hog, beef, sheep, and horse are available for oral and parenteral use. Preparations are made from the liver of one or several of these animal sources by methods described in detail in New and Nonofficial Remedies.[141]

The nature of the hematopoietic principle in liver was first investigated by Cohn and his colleagues.[103] It was found to be a nitrogenous base, probably of a polypeptide nature, which was readily soluble in water, insoluble in ether, and precipitable by acetone and strong alcohol. More recently, Dakin and West[104] derived a highly active substance from commercial liver extract which contained, besides amino acids, an aminohexose similar to glucosamine. Although the exact chemical nature of the antianemic principle in liver is still unknown, it

is reported to be free from lipids and protein.[105, 106] Its relationship to the allergenic principle in liver has not yet been determined.

Antigenicity of Liver Extract.—There have been relatively few investigations dealing with the antigenicity of liver extract. These studies have centered primarily upon the search for skin-sensitizing antibodies (reagins), with only a single reference to precipitins.

The most complete investigation was that by Criep[107] in a case of allergy to liver extract. The patient, an atopic male adult, had received liver (pork) injections over a period of one year without ill effects. After an interval of one month, treatment was resumed with the same preparation. The third injection was followed immediately by a severe attack of asthma and urticaria. However, the oral administration of concentrated liver extract was well tolerated, and this method of treatment was continued. One month after the reaction, a search for antibodies was made by direct test and by passive transfer. Positive cutaneous reactions were obtained with sheep, beef, chicken, and hog liver extracts. Positive transfer reactions for all of these preparations were obtained with dilutions of liver extract ranging as high as 1:100. Direct tests with the muscle and serum proteins of sheep, beef, chicken, and hog yielded negative results. Precipitins to liver extract were also present in serum dilutions up to 1:100. Passive sensitization of guinea pigs could not be effected with the serum. After an interval of three months, the cutaneous reactions were still positive and the precipitin and skin-sensitizing antibodies still demonstrable. At the end of ten months, by which time parenteral administration of liver extract had been resumed without untoward reactions, the studies were repeated. At this time the reagins and precipitins were no longer present, although the skin tests remained positive. Another retest after five years showed that the skin reaction was also negative.[93]

Additional information on reagins in relation to liver allergy appears in a recent report by Gray and Bowman.[108] Their patient was a nonatopic male adult who had received injections of liver extract for a period of about eighteen months. After an interval of one year, treatment was resumed. Injections were given every four days. Within an hour after the third injection urticaria and angioneurotic edema developed. Examination of the blood one week later revealed the presence of skin-sensitizing antibodies to liver extract. Positive transfer reactions were obtained with a 1:100 dilution of the liver extract. Treatment was discontinued. Examination of the serum after an interval of ten months still showed the presence of reagins by transfer test with a 1:100 dilution of liver extract.

In addition to the above reports, skin-sensitizing antibodies were sought in six other cases and were found in five.[109-113] Of the eight cases reported, only two were said to be atopic.[107, 113] In one of the latter,[113] skin-sensitizing antibodies were not found. The clinical manifestations

in this case, consisting primarily of an urticaria, did not differ materially from those observed in patients with reagins.

Despite the above evidences of the antigenicity of the liver allergen, hypersensitiveness to this excitant is by no means common, nor can it be induced at will. To demonstrate this fact, Criep[107] injected two atopic persons intramuscularly with 4 c.c. of liver extract semiweekly for four weeks without producing any evidence of sensitization. Two other atopic persons, injected intravenously with 4 c.c. of liver extract semiweekly for three months, also showed negative results. In addition, Criep tested five patients with pernicious anemia who had been receiving parenteral injections of liver extract over a period varying from one to three years. Negative cutaneous reactions were obtained with the liver extract.

Cutaneous Testing.—Cutaneous tests were performed by either the direct or the indirect (passive transfer) method in twelve cases of liver allergy. In all instances the intracutaneous technique was employed. Unfortunately, in direct testing, many of the investigators used 0.1 c.c. of the extract, thus impairing the reliability of the results obtained. Of the eleven patients tested directly, nine were reported to give positive reactions. Seven of these nine were also tested by the indirect method, and in every instance a positive reaction was obtained.

Positive reactions were obtained on direct testing with dilutions of liver extract ranging as high as 1:100,000.[107] As previously pointed out, positive cutaneous reactions were found to outlast the reagins in the circulation.[107] Gruen[110] reported positive cutaneous reactions persisting one year after the occurrence of the allergic reaction.

The immediate[110, 114] and delayed[111] reactions resulting from the intracutaneous tests have often been extremely severe and have assumed alarming proportions. Some have been reported equivalent in size to the palm of the hand.[110] The inflammatory processes following some of these reactions have persisted for as long as one month.[114]

Immediate constitutional reactions consisting of nausea, vomiting, diarrhea, and a marked edema of the entire arm have been observed in two cases[109, 110] following cutaneous tests with liver extract. In both these cases skin-sensitizing antibodies were found. The danger of employing 0.1 c.c. for intracutaneous testing in such cases is obvious.

Organ Specificity and Species Specificity in Relation to Liver Allergy.—Four patients with liver allergy showing positive direct and passive transfer reactions to liver extracts were also tested with the sera and the muscle protein extracts of the various animals from which liver extracts are prepared.[107, 110, 112, 113] In every instance, negative reactions were obtained, indicating that sensitivity to liver extract is not associated with species specificity, but is based upon an organ sensitivity.

The question of species specificity in relation to hypersensitiveness to liver extracts needs further study. The case reported by Krantz,[115]

which is frequently quoted as evidence of species specificity, is not convincing because of the absence of several essential points of information. This patient was said to have given a marked positive reaction on scratch test with horse muscle extract, but to have shown negative reactions to beef and pork proteins. The author suspected that the liver preparation which the patient had used previously and which had caused an allergic reaction had been derived from an equine source although definite information on this point was lacking. No cutaneous tests with any liver preparations were performed. No report is made as to whether the patient was also sensitive to horse serum.

Several instances of clinical allergy following the ingestion of liver are of interest in connection with this question. Rowe[116] reported the case of a patient who developed bronchial asthma following the ingestion of beef, hog, and lamb liver. Chicken liver, however, was said to be tolerated without ill effect. This experience differs from that of one of the writers (M. H.), who observed a case of severe asthma following the ingestion of beef, lamb, and chicken livers. The meats of these animals were well tolerated.

Clinical evidence of lack of species specificity in these conditions is supported by Criep's case of liver extract allergy.[107] His patient showed positive direct and transfer reactions to liver preparations derived from beef, sheep, hog, and chicken. The muscle and serum proteins of all these animals gave negative reactions in this patient.

Clinical Aspects.—Various types of reactions have been observed during the course of liver therapy. Not all of these were specific in etiology. Tansk,[117] in a review of this aspect of the question, has classified reactions following the administration of liver extract into four general types: (1) erythematous reactions; (2) histamine-like reactions; (3) acute reactions characterized by fall in blood pressure; and (4) allergic reactions. In view of the fact that histamine-like reactions are usually associated with a sharp drop in blood pressure, a differentiation between second and third types of reactions may be difficult. They, therefore, will be dealt with under one heading in the present discussion.

Erythematous reactions may involve the face, trunk, or entire body, or may be localized to the site of the injection. Tansk attributes such reactions to impurities in the preparations employed. Murphy[118] has frequently observed local erythematous reactions from 1 to 10 cm. in diameter appearing at the sites of subcutaneous injections of liver extract. The amount injected was not a factor in their etiology. The severity of these local reactions usually diminished as the liver therapy progressed. Flushing of the face following intramuscular injections of liver extract has been reported by Castle and Minot.[119] This has been associated occasionally with a fall in blood pressure. Erythematous reactions have at times preceded typical allergic reactions by a day or

more. Frequently these erythematous reactions do not develop until after injections of liver extract have been given for some time,[120] a fact which suggests the possibility that they may be allergic in some instances. This possibility is strengthened by Murphy's observations[118] that local erythematous reactions are most marked in patients who have had difficulty in taking liver by the oral route.

Despite attempts at purification of liver extract, most preparations for intravenous use still contain a vasodilator substance, which produces a temporary *fall in blood pressure* if injected at a rate exceeding 2 c.c. per minute.[119, 122] Heinsen[123] has reported that most German preparations of liver contain a histamine-like substance which is responsible for the fall in blood pressure which may follow their intravenous administration. This phenomenon is not observed regularly with subcutaneous or intramuscular injections of these substances. Koops[124] has demonstrated a cholinelike substance in another of the German preparations.

There is little doubt that some of the cases which have been reported as allergic reactions to liver extract really belong in the group of histamine-like reactions. The case cited by Vaughan and Pipes[125] in which the first intramuscular injection of liver extract was followed by cyanosis and shock appears to be of this type. Other cases of a similar nature have been described.[118, 126, 127, 140]

The chill or febrile reactions which are occasionally noted following the intravenous injection of liver extract have been attributed by Murphy[118] to the debilitated condition of the patient rather than to any allergenic factor in the liver preparation.

Excluding all of the reactions described above, there have been about twenty-eight cases reported in the literature in which what appeared to be *allergic reactions* were manifested. Among these there were seven patients with frank atopic histories. In view of the widespread use of liver therapy, this figure indicates a rarity of allergic reactions to this substance.

Allergic reactions, from the information available, have occurred in eight males and eight females. An analysis of twenty-two case records reveals the occurrence of one case in the second decade, seven in the third, four in the fourth, six in the fifth, two in the sixth, and two in the seventh. With two exceptions,[113] all such reactions have occurred in the white race.

In contrast to the findings in insulin hypersensitiveness, severe local reactions are uncommon following injections of liver extract.[110, 111, 119, 128, 169] Mild local reactions occasionally precede the onset of generalized urticarias.[114] The latter symptom is the one most frequently observed.[112, 113, 129, 130, 168] Associated with it, one may find angioneurotic edema,[131, 132] bronchial asthma,[5, 107, 115] nausea and vomit-

ing,[110, 114, 133] tachycardia,[134] vasomotor collapse,[111] dyspnea,[110, 112, 114, 120] and other manifestations. Such symptoms may occur individually or in combination.

An unusual reaction following the ingestion of liver preparations has been reported by Gardner.[135] In his patient, various liver preparations produced vertigo, palpitation, and menorrhagia; the symptoms could be produced at will. Definite evidence of the immunologic nature of the reaction is lacking.

Allergic reactions in some patients have been noted following both oral and parenteral administration of liver preparations.[134] In other cases parenteral administrations could not be tolerated, but liver preparations could be taken orally without difficulty.[115, 128, 130] In those patients in whom the ingestion of liver products caused untoward symptoms, reactions have been observed with raw liver,[136] cooked liver,[116, 131, 137] liver extracts,[131] and powdered liver preparations.[135]

In two atopic patients with bronchial asthma, the first intravenous injection of liver extract precipitated an attack of asthma.[122, 126] Because of the possibility that such reactions may have serious consequences, Castle and Minot[119] recommend that intravenous injections of liver extract should, if possible, be avoided in allergic patients. Whether the above asthmatic attacks were specific in nature or resulted from nonspecific stimulation of the shock organ cannot be determined from the available information. The possibility that these atopic persons may have been sensitized by the previous ingestion of liver as a food must be entertained.

With few exceptions, allergy to liver extract developed after this product had been tolerated without untoward reactions for some time. In some patients, symptoms of hypersensitiveness developed during the first course of treatment. Symptoms have been reported as appearing after the twelfth[133] or sixteenth injection,[115] or after from one[109, 131] to five[110, 120, 132] months of treatment. In other patients, the first series of injections produced no ill effects. Then, after an interval of from six weeks[5] to three years,[112-114, 134] during which time no treatment had been given, reactions developed during a second course of therapy. Symptoms were reported as early as the first injection[5] and as late as the thirty-eighth injection[112] in the second series of treatments.

Sensitivity to liver extract may persist for long periods of time. Von Herff[134] reported a case in which the injection of liver extract produced allergic symptoms similar to those which had occurred following the administration of this preparation one year earlier. In another patient,[130] parenteral administration of liver extract elicited urticaria and angioneurotic edema eight years after a previous allergic reaction, although this patient had tolerated oral administration of liver during this interval.

The occurrence of a *blood eosinophilia* during the course of oral or parenteral treatment with liver extracts has been observed fre-

quently.[131, 134] In some cases, the blood eosinophilia may reach from 30 to 60 per cent.[134] This has been interpreted by some observers as evidence of an allergy to the injected liver extract.[118, 134, 138, 139] It is interesting to note, however, that, in these patients in whom a blood eosinophilia was reported, no clinical symptoms of hypersensitiveness were manifested during the course of treatment with liver extracts. The significance of the high eosinophilic response in these patients is not yet clear.

Treatment.—When parenteral injections of liver extract result in allergic reactions, it has been advised that oral therapy be tried,[130] or that preparations from another animal source be substituted. It is unlikely that the latter measure will often meet with success, in view of the organ specificity which exists in most patients with true hypersensitiveness to liver. It may, however, be effective in patients in whom nonspecific factors play a part in the production of untoward symptoms.

"*Desensitization*" has been recommended by several authors in cases of liver allergy.[112, 114, 121] In the technique advised by Gruen,[110] small intracutaneous doses of a 1:1,000,000 dilution of liver extract were administered daily. Concentration of the extract was gradually increased, so that in three weeks intramuscular injections of undiluted extract were being tolerated. This type of procedure, however, has not been applied successfully in many cases.[130] Engel,[109] for instance, could not go beyond a 1:500 dilution because of the marked local reactions which resulted. The results obtained with these so-called methods of "desensitization" should be subject to guarded interpretation for reasons which have already been discussed in relation to insulin "desensitization."

Classification.—In view of the relatively few cases of liver allergy in which complete immunologic investigations have been reported, an attempt at classification of these reactions would be inadvisable. Despite the meagerness of the information, one gathers the impression that there are fewer resemblances to serum sickness among the allergic reactions to liver than were noted among the insulin cases. The tendency toward a "latent period" is less distinct. Severe local types of reactions are less frequent, and symptomatology in general is less characteristic of serum sickness. On the other hand, general reactions appear to occur with relatively greater frequency and reagins appear to occur with greater regularity and to persist longer than in insulin allergy. The majority of liver reactions seem to resemble some of the immediate types of acquired reactions encountered with horse serum. Undoubtedly, some of these reactions are atopic.

More case reports in which thorough immunologic investigations have been made are needed before conclusions can be drawn in regard to the mechanisms which are involved in liver allergy.

ALLERGY TO PITUITARY EXTRACT

Although pituitary extract is widely used, especially in the field of obstetrics, it is interesting to note that allergic reactions to it are rare.

Pituitary extracts are aqueous solutions prepared from the posterior lobes of the pituitary glands of freshly killed cattle and hogs. These preparations appear on the market under various trade names, such as solution posterior pituitary, pituitary liquid, pituitary extract, and pituitrin.[141]

The hormone of the posterior pituitary has not been isolated in crystalline form. Relatively pure, histamine-free preparations are available.[142] The oxytocic (pitocin, alpha-hypophamine) and the vasopressor (pitressin, beta-hypophamine) factors in pituitary extract have been prepared from the posterior lobe by Kamm and his associates.[143]

Immunologic Aspects.—Although more than twenty cases of allergic reactions to pituitary extract have been reported, detailed immunologic studies have been made in only a few. Specific skin-sensitizing antibodies for pituitary extract have been found in four patients.[144, 145] In one of these, passive transfer studies repeated four months later gave negative results, although positive cutaneous reactions were still present at this time.[145b] In another case, skin-sensitizing antibodies were first sought and demonstrated two years after the occurrence of the allergic reactions.[145b] Three other patients, studied for the first time one month, three months, and two years after the allergic reactions, failed to show the presence of reagins.[145b] It is not known, therefore, whether these antibodies had been present at the time of the reactions.

The reviewers could find no reports on precipitins or other types of antibodies to pituitary extract.

In some of the investigations, skin tests were made with different pituitary preparations by the scratch or intracutaneous technique. In this connection, Simon[145] recommended the use of pituitary extract in a dilution of 1:10 for direct and passive transfer testing in order to minimize the blanching which this substance produces in the skin. The preparations which he employed were freshly prepared and contained no preservative. He found positive cutaneous reactions in five patients with six different commercial preparations of pituitary extract.

Sensitivity was found to be organ specific and not species specific.[145b] In his five patients, Simon elicited positive cutaneous reactions with the pituitary extracts of cattle, hog, and dog, but found negative reactions with the muscle, pons, cortex, and blood serum of all of these animals. In three of these patients, human pituitary extracts produced positive reactions with the scratch technique. In the other two, scratch tests with human pituitary extracts were negative, but intracutaneous tests resulted in positive reactions. Extracts of other human organs, such as thyroid, pancreas and liver, produced negative results in all five patients.

Tests with serial dilutions of posterior pituitary extracts revealed a high degree of cutaneous sensitivity in some of the patients.[145b] Positive reactions could be elicited with dilutions as high as 1:1,000,000. The severity of the cutaneous reaction was proportional, not to the pharmacologic activity of the preparation, but to the amount of total solids it contained. This seemed to indicate that the antigenic principle in the pituitary extract was neither the vasopressor nor the oxytocic factor, but some other constituent of the glands.[145b] Certain fractions derived from the anterior pituitary gland, such as antuitrin-G and anterior pituitary extract, also gave positive reactions in some of these patients. No positive reactions were obtained with antuitrin-S.

In some of the patients with allergic reactions to pituitary extract, positive cutaneous reactions could be obtained from four months to two years later.[145b] Byrd,[146] however, found a rapid diminution of cutaneous sensitivity in his case. Positive cutaneous reactions were reported to have outlasted the skin-sensitizing antibodies in some cases.[145]

A review of the histories of the patients who had experienced allergic reactions to pituitary extracts reveals that most of them had received injections of these preparations on some previous occasion. In view of the common use of this medication, the paucity of case reports seems to indicate that induction of such sensitization is difficult. This was demonstrated by Simon and Ryder[145b] in various studies on pregnant women. Scratch and intracutaneous tests performed with a 1:10 dilution of pituitary extract on thirty primiparas at the time of delivery were all negative. Similar tests done nine days after the therapeutic administration of pituitary extract were still negative. Sixteen of these patients showed similar negative findings when retested after an interval of six weeks. Pendleton[144] likewise obtained negative reactions upon testing twenty-five pregnant women who had received pituitary extract during previous deliveries.

No information as to previous contact with pituitary extract is available in some of the reported cases of allergic reactions to this substance.[146-150] However, some of the multiparas in whom these reactions developed had had from one[144] to nine[145b] previous deliveries, at which times, according to their records, they had received injections of pituitary extract. Among nonobstetric cases, Hasson[151] reported a reaction after six injections which had been given over a period of three weeks. In the case of a male reported by Rowe,[116] the reaction followed the eighth injection. In another of his cases, an interval of eight months had elapsed between injections.

It is of interest in passing to note that negative cutaneous reactions to pituitary extracts were obtained in the infants of five mothers who manifested allergic reactions following the administration of pituitary extract after delivery.[144, 145b] All of these mothers showed positive reactions on direct test with pituitary extract, and four of them also gave

positive transfer reactions. Undoubtedly, the sensitization in these cases had occurred during previous pregnancies and the skin-sensitizing antibodies had been present throughout the period of gestation.

Clinical Aspects.—Only twenty-two case reports of allergic reactions to posterior pituitary extract have appeared in the literature, the earliest being that reported by Hasson[151] in 1930 and that by Brewer[148] in 1931. Pendleton,[144] reviewing the histories of 15,000 obstetric cases in his institution, could find only two instances of allergy to pituitary extract. Simon and Ryder,[145b] however, reported five cases from one hospital during a two-year period and suggested that this condition was probably more common than reports seemed to indicate. Not all of the instances of pituitary allergy occurred in obstetric cases.[116, 150-152]

Among the twenty-two reported cases, three[125, 145] had a previous personal history of atopic illnesses, and one gave a positive family history of allergy.[145b] Two others experienced bronchial asthma during their reactions to pituitary extract.[116, 144] All but one[116] of the patients were females. Most of them were between 20 and 40 years of age.

In interpreting the nature of reactions which may develop following an injection of pituitary extract, it is important to keep in mind the pharmacologic action of this preparation. It has pronounced effects on plain muscle, causing increased intestinal activity and uterine muscle contractions, and on the circulatory system, producing faintness, flushing, palpitation, headache, and changes in blood pressure.[142] Pendleton[144] points out that minute doses of pituitary extract do not produce the above pharmacologic reactions but may precipitate allergic symptoms. It is not unlikely that some of the cases[152, 153] reported in the literature as allergic reactions were actually examples of unusually severe pharmacologic responses to therapeutic doses of the drug.

In contrast to the frequent marked local reactions which occurred in insulin allergy, few were noted with pituitary extract.[150a, 154]

Generalized urticaria was the symptom most commonly observed in the allergic reactions to pituitary extract.[150a, 154-156] In one instance, this was purpuric in nature.[157] Other symptoms which were associated with the urticaria, or which occasionally occurred independently, included angioneurotic edema,[146, 151] bronchial asthma,[125, 150b] abdominal cramps,[149, 150b] nausea and vomiting,[146, 149, 156, 158] and collapse.[144, 150a, 152] Occasionally a severe generalized pruritus without urticaria was observed.[150b, 158] Reactions have been induced with as little as 1 minim[147, 149] of pituitary extract, even when given intracutaneously as a test.[144] No fatalities have resulted from any of these allergic reactions to pituitary extract.

In one instance, an immediate reaction consisting of generalized angioneurotic edema was followed after an interval of six days by a delayed reaction consisting of urticaria and simulating serum disease.[145b]

In some of the patients sensitive to posterior pituitary extract, positive cutaneous reactions to antuitrin-G were reported, but in no instance was a positive test obtained with antuitrin-S.[144, 145b] For this reason, the case mentioned by Vaughan and Pipes[125] is of interest. This patient, an atopic person with hay fever, developed urticaria, angioneurotic edema, cough, cyanosis, and shock following the parenteral administration of antuitrin-S. No information as to skin tests with this preparation was reported.

Treatment.—The allergic reactions induced by an injection of pituitrin can be controlled by the administration of epinephrine. Attempts at "desensitization" have not been reported, nor do there appear to be any indications for such procedures. Obstetric patients who develop allergic reactions to pituitary extract should not receive this medication in subsequent deliveries.[158]

ALLERGY TO PANCREATIC TISSUE EXTRACTS

Criep[93] has recently published the first report on acquired allergy to pancreatic tissue extract in two patients receiving intramuscular injections of this material. Pancreatic tissue extract is a purified acid-alcohol extract of deinsulinized beef pancreas which is being used therapeutically in thromboangiitis obliterans.

The cases cited were those of two males, aged 41 and 42 years, who had received several series of treatments with the pancreatic tissue extract. In one patient, an allergic reaction occurred during the second course of therapy. When treatment was resumed after another interval of one month, a milder but similar reaction occurred during the third series of injections. Two additional courses of injections were given at a later date, without untoward symptoms. In the second patient, a reaction occurred after injections were resumed following a treatment-free interval. In this patient also, further treatment was possible without ill effects.

In both cases, the allergic reactions included urticaria, pruritus, and angioneurotic edema. In addition, one patient, who had a history of chronic bronchitis, developed an attack of bronchial asthma as part of the general reaction.

Cutaneous tests with pancreatic tissue extracts resulted in positive reactions in both patients. Dilutions of 1:10 were employed for the tests, as undiluted tissue extracts were found to be irritating to the skin. Specific skin-sensitizing antibodies were demonstrated at the time of the allergic reactions. These antibodies persisted in the blood and could be demonstrated even when the patients were subsequently tolerating the injections of tissue extract without any untoward reactions. Criep, therefore, hesitates to regard the skin-sensitizing antibodies as the mechanism which mediates the allergic reaction. He considers them as immune bodies which are likely to occur incidently in these types of acquired allergy as they do in serum sickness.

Precipitin antibodies could not be found in the sera of these two patients, nor could these sera passively sensitize guinea pigs.

Additional passive transfer studies in human beings revealed the presence of specific skin-sensitizing antibodies for both beef and hog pancreas, but not for the muscle and serum of beef and hog. It is interesting to note that skin-sensitizing antibodies for chicken pancreas could not be detected in these sera, indicating a limited organ specificity.

Criep[93] was unsuccessful in his attempts to induce allergy to pancreatic tissue extract. He gave seven patients with peripheral vascular disease, including one atopic subject, repeated intramuscular injections of 3 c.c. of tissue extract once or twice weekly over a period of from four to twenty-four months. The negative findings in these experiments conform with the similar results obtained with insulin, liver, and pituitary extracts, which have been discussed in the previous sections.

ALLERGY TO ENZYMES

That enzymes may be etiological agents in allergic reactions is suggested by several reports in the literature.

A case recently reported by Maisel[162] was that of a pharmacist, a victim of ragweed hay fever, who developed rhinorrhea following the inhalation of caroid, pancreatin, and bile salts. Pepsin induced nasal and bronchial symptoms. Intracutaneous tests revealed slight positive reactions to pepsin, bile salts, and pancreatin. Skin-sensitizing antibodies for pancreatin only could be demonstrated. Tests with hog protein, the animal source of both pancreatin and pepsin, gave negative results.

There are several reports in the literature of clinical sensitivity to pancreatin by inhalation.[116, 163-165] Positive skin tests were obtained with high dilutions of this substance in some of these patients. The absence of information as to the nature of the testing material and the failure to look for skin-sensitizing antibodies limit the value of these observations. In one case of alleged sensitivity to pancreatin and trypsin, the patient was found to be acutely sensitive to pork, the probable source of these preparations.[116]

In addition to Maisel's report of allergy to pepsin noted above, a case of clinical sensitivity to this substance was also reported by Beecher.[164] This patient showed a positive cutaneous reaction to pepsin and peptenzyme and a negative reaction to pork. No search for reagins was made.

The possibility that sensitivity to amylopsin may occur is suggested in the case reported by Cohen and Simon.[6] Their nonatopic patient developed local edema and generalized urticaria following injections of commercial insulins. He showed positive cutaneous reactions to beef and pork insulins, and skin-sensitizing antibodies for pork insulin were detected in his serum. The patient, however, showed negative reactions

to crystalline insulin and could tolerate injections of it without difficulty. Continuing the search for the offending factor in the commercial insulin preparations, Cohen and Simon obtained negative reactions to beef and pork, and to pituitary, thyroid, and ovarian extracts derived from these sources. Deinsulinized pork pancreas produced a positive reaction, and trypsin gave a negative or doubtful reaction. Amylopsin, however, both by scratch and intracutaneous techniques, gave marked reactions. The same tests performed on normal control subjects produced negative results. Unfortunately, the search for reagins to amylopsin was not reported in this case. The evidence, however, favors the probability that amylopsin was the allergenic factor involved.

ALLERGY TO ESTROGENIC SUBSTANCES

Despite the extensive use of estrogenic substances during the past few years, reports of allergic reactions to these preparations are rare in the literature.

Loftis[159] has recently reported the case of a patient with purpuric lesions of the thigh which, in his opinion, were definitely due to the estrogenic substance and not to the vehicle employed.

Two instances of allergic reactions following the use of estrogenic substances have recently been brought to the reviewers' attention.[161] In one case, a localized urticaria and a marked induration were noted after the fourth weekly intramuscular injection of 4,000 R.U. of amniotin. An injection of sesame oil, the vehicle in this preparation, produced no reaction. Oral medication was then prescribed in the form of 600 R.U. of progynon D.H. (synthetic alpha-estradiol-benzoate) to be taken every third day. After two doses, urticaria developed on the buttocks, where the intramuscular injections had been given. One week later, after the fifth dose of progynon, generalized urticaria and angioneurotic edema developed, necessitating the use of epinephrine. The ingestion of a crystalline preparation of the hormone also produced a typical general reaction. Tablets devoid of the hormone produced no ill effects. Oretone (testosterone propionate) was then administered at weekly intervals and tolerated for several months without untoward effects. Cutaneous tests with animal proteins were performed, with uniformly negative results. Cutaneous tests with the hormone preparations were not done.

In another patient, marked local induration developed after the fourth intramuscular injection of progynon-B, which was being administered twice weekly. Progynon D.H. tablets were then prescribed for oral use. The first dose was followed by a recurrence of erythematous-edematous reactions at the sites of the intramuscular injections. Treatment was then discontinued. Skin tests were not performed in this case.

In the evaluation of reactions following the injection of estrogenic substances, it is well to keep in mind the case reported by Levison and Harrison.[160] The patient, who developed a severe dermatitis from injections of theelin and estrone, gave the same reactions when tested intracutaneously with the oily vehicles employed in the estrogenic preparations. The authors believed these to be the offending factors in the reactions observed in their patient.

MISCELLANEOUS

Cohen and Waterstone[166] have recently reported two cases of alleged sensitivity to epinephrine and have reviewed the literature on this subject. Most of the reports dealt with instances of necrosis, which probably resulted from vasoconstriction and tissue anemia, or from the toxic effects of the anesthetics contained in epinephrine solutions. Other reported reactions were probably examples of exaggerated pharmacologic responses to this medication. In their own report, Cohen and Waterstone cited the histories of two colored patients with bronchial asthma, who reacted with severe swellings at the site of epinephrine injections. This inflammatory reaction came on within one-half hour and then gradually subsided. Within from four to seven days, an ulceration about 1 cm. in diameter appeared at these sites. A pigmented area remained after the inflammatory reaction subsided. Neither case developed a local reaction following the subcutaneous injection of synthetic epinephrine hydrochloride or of the various preservatives in epinephrine solutions. In one case the unintentional injection of the epinephrine into a small blood vessel was followed by a flare-up of the unhealed sites of the previous injections. No reagins for epinephrine could be demonstrated in the sera of either patient. Negative skin tests were obtained with beef and pork in both cases. Patch tests with solutions and crystals of epinephrine, sodium bisulfate, and chloretone were negative. There is little evidence to justify the conclusion that the above reactions were immunologic in nature.

According to Rowe,[116] there has been no reported instance of allergy to the animal source of epinephrine in patients receiving this medication.

Greenbaum[167] has recently reported two cases with extensive local reactions following the subcutaneous injections of histaminase. In both instances, the first subcutaneous injection was well tolerated. In one case, the marked local reaction occurred from eight to twenty-four hours after the second injection. In the other patient, a treatment-free interval of one month had elapsed between injections. Continued therapy in the latter case was followed by severe abdominal cramps, nausea, and diarrhea. No tests were made with pork, from which the histaminase was derived. Pork sensitivity has obviously been the cause for many of the allergic reactions to histaminase which have been encountered.

REFERENCES

1a. Jensen, H.: Insulin, Its Chemistry and Physiology, New York, 1938, Commonwealth Fund.

b. Jensen, H., Wintersteiner, O., and Geilung, E. M. K.: Studies on Crystalline Insulin; The Isolation of Crystalline Insulin From Fish Islets (Cod and Pollock) and From Pig's Pancreas; Activity of Crystalline Insulin and Further Remarks on Its Preparation, J. Pharmacol. & Exper. Therap. **36**: 115, 1929.

c. Jensen, H., Evans, E. A., Jr., Pennington, M. D., and Schock, E. D.: Action of Various Reagents on Insulin, J. Biol. Chem. **114**: 199, 1936.

d. Jensen, H.: The Chemical Study of Insulin, Science **75**: 614, 1932.

2a. Abel, J. J.: Crystalline Insulin, Proc. Nat. Acad. Sc. **12**: 132, 1926.

b. Abel, J. J., and Geilung, E. M. K.: Researches on Insulin. I. Is Insulin an Unstable Sulphur Compound? J. Pharmacol. & Exper. Therap. **25**: 423, 1925.

c. Abel, J. J., Geilung, E. M. K., Rouiller, C. A., Bell, F. K., and Wintersteiner, O.: Crystalline Insulin. J. Pharmacol. & Exper. Therap. **31**: 65, 1927.

3. Scott, D. A.: Further Studies on Crystalline Insulin, J. Biol. Chem. **92**: 281, 1931.

4. Shonle, H. A., and Waldo, J. H.: Some Chemical Reactions of the Substance Containing Insulin, J. Biol. Chem. **58**: 731, 1924.

5. Vaughan, W. T.: Practice of Allergy, St. Louis, 1939, The C. V. Mosby Co.

6. Cohen, A. E., and Simon, F.: Insulin Hypersensitivity, J. ALLERGY **9**: 503, 1938.

7. Hagedorn, H. C., Jensen, B. N., Krarup, N. B., and Wodstrup: Protamine Insulinate, J. A. M. A. **106**: 177, 1936.

8. Kern, R. A., and Langerer, P. H., Jr.: Protamine and Allergy. I. Nature of the Local Reactions After Injections of Protamine Zinc Insulin. II. Induction of Sensitivity to Insulin by Injections of Protamine Zinc Insulin. J. A. M. A. **113**: 198, 1939.

9. Wells, H. G.: The Chemical Aspects of Immunity, New York, 1929, Chemical Catalog Co.

10. Taylor, A. E.: Chemical Studies in Cytolysis, J. Biol. Chem. **5**: 311, 1908.

11. Ornstein, F., and Mera, R.: Ueber Faellungen von Insulin mit normalen Serum, Wien. klin. Wchnschr. **39**: 840, 1926.

12. Wasserman, P., Broh-Kahn, R. H., and Mirsky, I. A.: The Antigenic Properties of Insulin, J. Immunol. **38**: 213, 1940.

13. Bernstein, C., Kirsner, J. B., and Turner, W. J.: Studies on Anaphylaxis With Insulin, J. Lab. & Clin. Med. **23**: 938, 1938.

14. Clutton, R. F., Harrington, C. R., and Yuill, M. E.: Studies in Synthetic Immunochemistry. I. Serological Investigation of O-B Glucosidotyrosyl Derivative of Proteins, Biochem. J. **32**: 1111, 1938.

15. Duenner, L., and Dohrn, M.: Klinische und experimentelle Untersuchungen ueber die Wirkung des Insulins bei Lungentuberkulose, Med. Klin. **24**: 1182, 1928.

16a. Cade, A., Barral, P., and Roux, J.: À propos des éruptions cutanées d'origine insulienne, Presse méd. **39**: 1917, 1931; Also Bull. Soc. franç. de dermat. et syph. **37**: 67, 1930.

b. Barral, P., and Roux, J.: L'insuline constitue-t-elle en ellemême un antigéne spécifique, Compt. rend. Soc. de biol. **106**: 292, 1931.

17. Lewis, J. H.: The Antigenic Properties of Insulin, J. A. M. A. **108**: 1336, 1937.

18. Raynaud, M., and Lacroix, A.: Un cas d'anaphylaxis à l'insuline essai de pathogénes des oedemes insuliens, Bull. et mêm. Soc. méd. d. hôp. de Paris **49**: 831, 1925.

19. Tuft, L.: Insulin Hypersensitiveness. Immunologic Considerations and Case Reports, Am. J. M. Sc. **176**: 707, 1928.

20. Karr, W. G., Kreidler, W. A., Scull, W. A., and Petty, O. H.: Certain Immunologic Studies in Insulin Sensitivity, Am. J. M. Sc. **181**: 293, 1931.

21. Fiandaca, S.: Fenomeni Anafilattica da Insulina, Riforma Med. **49**: 1423, 1933.

22. Cannon, P. R., and Marshall, C. E.: An Improved Method for the Determination of the Precipitative Titers of Antisera, J. Immunol. **38**: 365, 1940.

23. Richardson, R.: Complement Fixation With Insulin as Antigen, Proc. Soc. Exper. Biol. & Med. **38**: 874, 1938.

24. Campbell, W. R., Gardner, W. J., and Scott, D. A.: Reactions After Administration of Crystalline Insulin, J. Clin. Investigation **9**: 28, 1930.

25. Gilberto, A., and Benavides, M.: Alergia Insulinica. (Reporte de un Caso de Hipersensibilidad a la Insulina, Vida nueva **39:** 179, 1937.
26. Grishaw, W. H.: Allergic Manifestations to Insulin, J. A. M. A. **97:** 1885, 1931.
27. Lasch, F.: Ueber Insulinanaphylaxie, Med. Klin. **31:** 975, 1935.
28. Battistini, G.: La Sensibilizzazione all'insulina, Clin. med. ital. **63:** 125, 1932.
29. Herzog, K.: Beobachtungen ueber Insulin-Ueberempfindlichkeit und den Wert intracutaner Vertraeglichkeits-pruefungen fuer die Insulintherapie, Ztschr. f. klin. Med. **136:** 297, 1939.
30. Sammis, F. E.: Hypersensitiveness to Insulin, J. ALLERGY **6:** 387, 1935.
31. Bryce, L. M.: Hypersensitiveness to Insulin, M. J. Australia **1:** 371, 1933.
32. Allan, F. N., and Scherer, L. R.: Insulin Allergy, Endocrinology **16:** 417, 1932.
33. Antonini, Fr.: Les réactions cutanées de l'insuline, Thése de la Faculté de méd. de Paris, July, 1925.
34. Murphy, J. A., Beardwood, J. P., and Miller, M. M.: Report on Insulin Sensitivity With Passive Transfer, J. ALLERGY **5:** 606, 1934.
35. Blotner, H.: Late Results Following the Use of Insulin in One Hundred Cases of Malnutrition, New England J. Med. **218:** 371, 1938.
36. Herzstein, J., and Pollack, H.: Insulin Allergy; Case Report With Review of the Literature, J. Mt. Sinai Hosp. **6:** 3, 1939.
37. Wilder, R. M.: Clinical Diabetes Mellitus and Hyperinsulinism, Philadelphia, 1940, W. B. Saunders Co.
38. Fowler, A. F., Bensley, E. H., and Rabinowitch, I. M.: Control of Diabetes Mellitus With Protamine Zinc Insulin in Surgery (Based Upon a Study of 25 Cases), Canad. M. A. J. **36:** 561, 1937.
39. Mauriac, M.: Un cas de sensibilisation à l'insuline chez une petite fille, Paris méd. **55:** 372, 1925.
40. Lerebouillet, P., Lelong, M., and Frossard, R.: Un cas de diabéte infantile traité par l'insulin avec accidents cutanées graves: l'erythrodermie oedemateuse insulienne, Bull. et mém. Soc. méd. d. hôp. de Paris **48:** 1184, 1924.
41. Rackemann, F. M.: Clinical Allergy, Particularly Asthma and Hay Fever, New York, 1931, Macmillan Co.
42. Herold, A. A.: Insulin Allergy: Report of Seven Cases With Successful Desensitization, New Orleans M. & S. J. **91:** 163, 1938.
43. Stoetter, G.: Desensibilisierungserfolg bei einem hochgradig insulinallergischen Diabetiker, Klin. Wchnschr. **16:** 1180, 1937.
44. Johnson, A. S.: Arthritis as a Possible Manifestation of Allergy to Insulin, New England J. Med. **211:** 321, 1934.
45. Bose, J. P.: Insulin Anaphylaxis, Indian M. Gaz. **72:** 465, 1937.
46. Corcoran, A. C.: Note on Rapid Desensitization in a Case of Hypersensitiveness to Insulin, Am. J. M. Sc. **196:** 359, 1938.
47. Glassberg, B. Y., Somogyi, M., and Taussig, A. E.: Diabetes Mellitus; Report of Case Refractory to Insulin, Arch. Int. Med. **40:** 676, 1927.
48. Joslin, E. P.: Treatment of Diabetes Mellitus, Philadelphia, (a) 1928, (b) 1935, (c) 1937, Lea & Febiger.
49. Swern, N.: Influence of Diabetes Mellitus in Asthmatic Patients, J. ALLERGY **2:** 375, 1931.
50. Kern, R.: Studies in Heredity in Allergy and in Diabetes, Tr. A. Am. Physicians **49:** 23, 1934.
51. Ulrich, H., Hooker, S. B., and Smith, H. H.: Allergic Reaction to Insulin, New England J. Med. **221:** 522, 1939.
52. Strooman, G.: Anaphylaktische Erscheinungen nach Injektion von Insulin (Brand), Med. Klin. **26:** 1523, 1930.
53. Lasersohn, M.: Local Insulin Reactions, J. A. M. A. **95:** 199, 1930.
54. Sturtevant, M.: Local Anaphylaxis Following Injection of Insulin, J. A. M. A. **82:** 964, 1924.
55. Bernard, A.: Sur l'intolerance à l'insuline et son traitement, J. de Sc. méd. de Lille **45:** 85, 1927.
56. Blaisdell, E. R.: Allergic Reactions to Insulin, Maine M. J. **22:** 129, 1931.
57. Hunscheidt, H.: Calcium bei Insulinueberempfindlichkeit, Zentralbl. f. inn. Med. **55:** 369, 1934.
58. Malten, H.: Bekaempfung der Insulin-Allergie, München. med. Wchnschr. **85:** 166, 1938.
59. Hajek, J.: Local Insulin Reactions, J. A. M. A. **96:** 193, 1930.
60. Hulst, L. A.: Plaatselijke Infiltraten na Insulinetoediening, Nederl. tijdschr. geneesk. **75:** 5278, 1931.

61. Allan, F. N., and Scherer, L. R.: Insulin Resistance Due to Allergy, Am. J. M. Sc. **185:** 815, 1933.
62. Vedel, M., Puech, and Reverdy: Urticaria provoqué par l'insuline. Accident anaphylactique, Bull. Soc. d. sc. méd. Montpellier **6:** 262, 1925.
63. Hansen, K., and Eyer, H. V.: Insulin-Allergie, Deutsches Arch. f. klin. Med. **174:** 133, 1932.
64. Nonn, H.: Insulinallergie und ihr Einfluss auf die diabetische Stoffwechsellage, München. med. Wchnschr. **80:** 1597, 1933.
65. Jeanneret, R.: Une application pratique de la méthode de désensibilisation par les cuti-réactions répetées. Urticaire à l'insuline, Rev. méd. de la Suisse Rom. **49:** 99, 1929.
66. Krauepl, F.: Insulinallergie und ihr Einfluss auf die diabetische Stoffwechsellage, München. med. Wchnschr. **80:** 1248, 1933.
67. Schill, E.: Ueber die Vermeidung des im Laufe der Insulinbehandlung anaphylaxieaehnlichen Zustaendes, Therap. d. Gegenw. **33:** 146, 1931.
68. Davidson, M. J.: Insulin Allergy. A Review of Recent Literature and Report of a Case, J. ALLERGY **6:** 71, 1935. Discussion by Huber, H. L.
69. von Grafe, E.: Probleme der Insulintherapie, München. med. Wchnschr. **83:** 1255, 1936.
70. Kaufmann, E.: Nebenerscheinungen bei der Insulinanwendung, Deutsche. med. Wchnschr. **56:** 1955, 1930.
71. Laurence, R. D.: Local Insulin Reactions, Lancet **1:** 1125, 1925.
72. Collens, W. S., Lerner, G., and Fialka, S.: Insulin Allergy. Treatment With Histamine, Am. J. M. Sc. **188:** 528, 1934.
73. Desgrez, A., Rathery, F., and Bierry, H.: Titrage et posologie de l'insuline, Paris méd. **51:** 423, 1924.
74. Davidson, M. T.: A Case of Urticaria Due to Insulin Sensitization, J. ALLERGY **4:** 74, 1932.
75. Greiff, W.: Zur Behandlung der Uberempfindlichkeit gegen Insulin, Klin. Wchnschr. **10:** 1955, 1931.
76. Grote, L. R.: Neuzeitliche Diabetesbehandlung, Ergebn. d. ges. Med. **18:** 301, 1933.
77. Rudy, A.: Urticaria and Insulin Resistance With Reference to the Relation of the Skin to Carbohydrate Metabolism. Report of Case and Review of the Literature, New England J. Med. **204:** 791, 1931.
78. Walker, S. E.: Report of a Case of Diabetes Mellitus With Anaphylaxis Following the Hypodermic Injection of Insulin, U. S. Vet. Bur. M. Bull. **2:** 700, 1926.
79. Allan, F. N., and Scherer, L. R.: Insulin Allergy. Proc. Staff Meet., Mayo Clinic **7:** 204, 1932.
80. Baker, T. W.: A Clinical Survey of One Hundred and Eight Consecutive Cases of Diabetic Coma, Arch. Int. Med. **58:** 373, 1936.
81. Engelberg, J.: Ein Fall von Insulinanaphylaxie, Med. Klin. **1:** 212, 1927.
82. Falta, W.: Die Zuckerkrankheit, Berlin, 1936, Urban & Schwarzenberg.
83. Strauss, H.: Ueber Insulin Resistente Diabetiker, Klin. Wchnschr. **4:** 491, 1925.
84. Schenck, V.: Ueber Insulin-Dermatitis, Deutsche med. Wchnschr. **58:** 1605, 1932.
85. Bonem, P.: Nebenwirkungen von Insulin, München. med. Wchnschr. **76:** 1585, 1929.
86a. Williams, J. R.: Allergic Insulin Reactions. Report of a Case Exhibiting Severe Gastro-Intestinal Allergic Reactions Following Injections of Insulin, J. A. M. A. **94:** 1112, 1930.
b. Williams, J. H.: A Second Case of Gastro-Intestinal Allergy Due to Insulin, J. A. M. A. **100:** 658, 1933.
87. Bayer, L. M. F.: Desensitization to Insulin Allergy, J. A. M. A. **102:** 1934, 1934.
88. Joslin, E. P., Root, H. F., White, P., Marble, A., and Joslin, A. P.: Protamine (Zinc) Insulin, Med. Clin. North America **22:** 711, 1938.
89. Stilwell, G. R.: Neutralization of Insulin Before Injection. Brit. M. J. **2:** 465, 1924.
90. Achard, C., and Bloch, S.: Diabéte avec coma guére par l'insuline. Accidents d'anaphylaxie et pyohêmie consécutive, Bull. et mém. Soc. méd. d. hôp. de Paris **40:** 1210, 1925.
91. Katsch, G.: Verhandl. d. deutsch. Gesellsch. f. inn. Med. **44:** 469, 1932.
92. Hirsch-Kauffmann, H.: Ueber Insulinschaeden, Therap. d. Gegenw. **71:** 259, 1931.
93. Criep, L. H.: Allergy to Tissue Extract With Report of Two Cases. In press.

94. Umber, F., and Rosenberg, M.: Weitere Erfahrungen mit Insulin an hundert klinisch behandelten Diabetikern, Deutsche med. Wchnschr. **50**: 359, 1924.
95. Hallerman, A.: Nebenerscheinungen bei der Insulinanwendung, Deutsche med. Wchnschr. **56**: 1611, 1930.
96. Wechsler, L.: Beitrag zur Aetiologie und Therapie der Insulinueberempfindlichkeit bei Diabetes, Wien. klin. Wchnschr. **37**: 1115, 1932.
97. Rynearson, E. H.: Practical Suggestions for the Use of Protamine-Zinc Insulin, Med. Clin. North America **23**: 1099, 1939.
98. Strasser, A.: Insulinbehandlung unter Kalkaufladung, Med. Klin. **27**: 695, 1931.
99a. Roth, G. M., and Rynearson, E. H.: The Use of Histamine and Histaminase in the Treatment of Allergic Reactions to Insulin, Proc. Staff Meeting, Mayo Clin. **14**: 353, 1939.
b. Roth, G. M., and Horton, B. T.: Histaminase: Physiologic Effects on Man and Its Therapeutic Value in Medicine, Bull. New York Acad. Med. **16**: 570, 1940.
100. Harten, M., and Walzer, M.: Serum Allergy, J. ALLERGY **2**: 1, 1939.
101. Minot, G. R., and Murphy, W. P.: Treatment of Pernicious Anemia by a Special Diet, J. A. M. A. **87**: 470, 1926.
102. Gaensslen, M.: Ein hochwirksamer injizierbarer Leberextrakt, Klin. Wchnschr. **9**: 2099, 1933.
103. Cohn, E. J., Minot, G. R., Alles, G. A., and Salter, W. T.: The Nature of Material in Liver Effective in Pernicious Anemia, J. Biol. Chem. **77**: 325, 1928.
104. Dakin, H. D., and West, R.: Observations on Chemical Nature of Hematopoietic Substance Occurring in Liver, J. Biol. Chem. **109**: 489, 1935.
105. Whitby, L. E. H., and Britton, C. J. C.: Disorders of the Blood, Philadelphia, 1939, The Blakiston Co.
106. Best, C. H., and Taylor, N. B.: The Physiological Basis of Medical Practice, Baltimore, 1937, William Wood & Co.
107. Criep, L. H.: Allergy to Liver Extract, J. A. M. A. **110**: 506, 1937.
108. Gray, I., and Bowman, K. L.: In press.
109. Engel, K.: Anafilaxia a los Preparadas di Higado en un caso di anemia Perniciosa, Bol. Assoc. méd. de Puerto Rico **25**: 326, 1933.
110. Gruen, G.: Ueberempfindlichkeit gegen parenteral verabreichte Leberpraeparate bei einem Fall von pernizioeser Anaemie, Wien. klin. Wchnschr. **47**: 751, 1934; also Orvosi hetil. **77**: 736, 1933.
111. Lasch, F.: Ueber allergische Symptome bei parenteraler Lebertherapie, Wien. med. Wchnschr. **86**: 126, 1936; also Med. Klin. **31**: 1623, 1935.
112. Pache, H. D.: Beobachtungen bei einer Allergie gegen Leberextrakte, Deutsche med. Wchnschr. **65**: 1192, 1939.
113. Jones, C. A.: Allergic Reactions Following the Parenteral Administration of Liver, Extract, New Internat. Clin. **3**: 259, 1939.
114. Diena, D.: Ipersensibilita a preparati epatici, Gior. d. r. Accad. di med. di Torino **101**: 462, 1938.
115. Krantz, C. I.: Anaphylactic Reactions Following Medication With Parenteral Liver Extract. J. A. M. A. **110**: 802, 1938.
116. Rowe, A. H.: Clinical Allergy Due to Foods, Inhalants, Contactants, Fungi, Bacteria and Other Causes: Manifestations, Diagnosis and Treatment, Philadelphia, 1937, Lea and Febiger.
117. Tansk, M.: Bijreacties na insiuting van Leverextracten, Nederl. tijdschr. v. geneesk. **80**: 749, 1936.
118. Murphy, W. P.: The Parenteral Use of Liver Extract in Pernicious Anemia, J. A. M. A. **98**: 105, 1932.
119. Castle, W. B., and Minot, G. R.: Pathology, Physiology and Clinical Description of the Anemias, New York, 1936, Oxford University Press.
120. Geijskes, P. A. G.: Onaangename Verschijnsllen na Toldiening van Pernaemon, Nederl. tijdschr. v. geneesk. **30**: 1915, 1936.
121. Milbrodt, W.: Ueber eine eigenartige scheinbare Allergie gegen Leberextrakt, Dermat. Wchnschr. **101**: 1595, 1935.
122. Castle, W. B., and Taylor, F. H. L.: Intravenous Use of Liver Extract, J. A. M. A. **96**: 1198, 1931.
123a. Heinsen, H. A.: Chemische Untersuchungen an Leberpraeparaten des Handels auf kreislaufwirksame Substanzen, Klin. Wchnschr. **12**: 1722, 1933.
b. Heinsen, H. A., and Wolf, H. J.: Der Einfluss koerpereigener Substanzen auf den Bludruck beim Menschen: IV. Die Wirkung von Leberpraeparaten bei intravenoeser Verabreichung, Klin. Wchnschr. **13**: 523, 1934.

124. Koops, W. S., Dingemanse, E., and Luwisch, D.: Ueber Blutdruckbeeinflussende Stoffe in Leberpraeparaten, Acta brev. Neerland. **5:** 70, 1935.
125. Vaughan, W. T., and Pipes, D. M.: On the Probable Frequency of Allergic Shock, Am. J. Digest. Dis. **3:** 558, 1937.
126. Queries and Minor Notes: Possible Sensitivity to Liver Extract, J. A. M. A. **104:** 2019, 1935.
127. Klinhert, D.: Onaangename Verschijnselen Na Pernaemoninspiuting, Nederl. tijdschr. v. geneesk. **79:** 5751, 1935.
128. Strandell, B., and Hammar, E.: "Magenresistente" Faelle von Anaemia perniciosa erfolgreich mit Campolon behandelt: Urtikaria als Komplikation, Acta med. Scandinav. **77:** 345, 1932.
129. Bloom, M.: Sensitivity to Liver Extract, J. A. M. A. **105:** 223, 1935.
130. Queries and Minor Notes: Sensitivity to Liver Preparations, J. A. M. A. **115:** 1121, 1940.
131. Held, I. W., and Goldbloom, A. A.: Addison-Biermer's Anemia (Pernicious Anemia): Report of Case Showing Allergic-Like Phenomena to Liver Extract, J. A. M. A. **96:** 1361, 1931.
132. Roovers, J. J. C. P. A.: Onaangename verschijnselen na Pernaemoninspiutingen, Nederl. tijdschr. v. geneesk. **79:** 5148, 1935.
133. Murphy, W. P.: Maintenance of Normal Blood in Pernicious Anemia by Means of Intramuscular Injections of a Solution of Liver Extract, Am. J. M. Sc. **186:** 271, 1933.
134. Von Herff, D.: Die klinische Bedeutung der Arzneimittel als Antigene. Sogenannte Arzneimittelidiosynkrasien, Leipsig, 1937, G. Thieme.
135. Gardner, J. W.: Allergy to Oral Administration of Liver Concentrate, J. A. M. A. **110:** 2003, 1938.
136. Matzger, E.: Bronchial Asthma Caused by Liver and Liver Extract Diet in a Patient Suffering from Primary Anemia, J. A. M. A. **96:** 110, 1931.
137. Schlesinger, W.: Zur Frage der Leberbehandlung bei pernizioeser Anaemie als diaetetischer Reiztherapie, Wien. med. Wchnschr. **80:** 696, 1930.
138. Trappen, von der: München. med. Wchnschr. **80:** 700, 1933.
139. Kaemmerer, H.: München. med. Wchnschr. **80:** 582, 1933.
140. Knipers, F. C.: Overgevoeligheidsreactie na Leverinspiuting, Nederl. tijdschr. v. geneesk. **79:** 2771, 1935.
141. New and Nonofficial Remedies, Chicago, 1939 and 1940, American Medical Association.
142. Abel, J. J.: Physiological, Chemical and Clinical Studies on Pituitary Principles, Harvey Lectures, 1934, p. 154.
143. Kamm, O., Aldrich, T. B., Grote, I. W., Rowe, L. W., and Bugbee, E. P.: The Active Principle of the Posterior Lobe of the Pituitary Gland, J. Am. Chem. Soc. **50:** 573, 1928.
144. Pendleton, G. F., Ball, W. G., and Rhode, W.: Hypersensitivity to Pituitary Extract. J. Missouri M. A. **34:** 194, 1937.
145a. Simon, F. A.: Hypersensitiveness to Pituitary Extract, J. A. M. A. **104:** 996, 1935.
b. Simon, F. A., and Ryder, C. F.: Hypersensitiveness to Pituitary Extract, J. A. M. A. **106:** 512, 1936.
146. Byrd, H. G.: Anaphylaxis Following Administration of Pituitrin, Virginia Med. Monthly **61:** 713, 1935.
147. Abbett, A. L.: Sensitivity to Solution of Posterior Pituitary, J. A. M. A. **114:** 821, 1940.
148. Brewer, J. S.: Sensitivity to Solution of Posterior Pituitary, J. A. M. A. **114:** 678, 1940.
149. McMann, W.: Hypersensitivity to Solution of Posterior Pituitary, J. A. M. A. **113:** 1488, 1939.
150a. Seligman, B.: Hypersensitivity to Solution of Posterior Pituitary, J. A. M. A. **114:** 272, 1940.
b. Seligman, B.: Hypersensitivity to Solution of Posterior Pituitary, J. A. M. A. **114:** 344, 1940.
151. Hasson, J.: Anaphylaxis Following Injection of Pituitary Extract, Brit. M. J. **1:** 242, 1930.
152. McMann, W.: Pituitary Shock, Am. J. Obst. & Gynec. **31:** 1047, 1936.
153. La Haye and Peters: Le déchlenchement du travail par injections intramusculaires de doses fractionnées d'extract hypophysaire postérior, Rev. franç. de gynéc. et d'obst. **25:** 555, 1930; also Strasbourg méd. **90:** 490, 1930.
154. Paolazzi, G. E.: Reaction to Solution of Posterior Pituitary, J. A. M. A. **114:** 823, 1940.

155. Queries and Minor Notes: Sensitivity to Pituitary Extract, J. A. M. A. **105:** 904, 1935.
156. Wang, P. W., and Maxwell, J. P.: Protein Shock After the Administration of Pituitrin, Chinese M. J. **47:** 66, 1933.
157. Koons, F. W.: Anaphylactic Shock From the Use of Pituitrin in an Obstetric Case, J. Kansas M. Soc. **36:** 323, 1935.
158. Rydburg, W. C.: Hypersensitivity to Pituitary, J. A. M. A. **113:** 1981, 1939.
159. Loftis, E. L.: Purpura Due to Injection of Estrogenic Substance, Arch. Dermat. & Syph. **42:** 138, 1940.
160. Levison, L. A., and Harrison, J. J.: Severe Allergic Dermatitis Following the Parenteral Use of Theelin, J. A. M. A. **113:** 2055, 1939.
161. Birnberg, C., and Golan, H.: Personal communication.
162. Maisel, F. E.: Pepsin Allergy: Case Report, J. ALLERGY **11:** 607, 1940.
163. Coca, A. F., Walzer, M., and Thommen, A. A.: Asthma and Hay Fever in Theory and Practice, Springfield, Ill., 1931, Charles C. Thomas, p. 449.
164. Beecher, W. L.: Hyperesthetic Rhinitis and Asthma Due to Digestive Ferments, Illinois M. J. **59:** 343, 1931.
165. Peshkin, M. M.: Bronchial Asthma and Other Allergic Manifestations in Pharmacists, J. A. M. A. **82:** 1854, 1924.
166. Cohen, A. E., and Waterstone, M. L.: Epinephrine Hypersensitivity: Report of Two Cases, J. ALLERGY **11:** 393, 1940.
167. Greenbaum, S. S.: Local Anaphylactic (Arthus?) Phenomena From Parenteral Injections of Histaminase, J. A. M. A. **115:** 847, 1940.
168. Parrisius, W., and Lohmeyer, A.: Behandlung der pernizösen Anämie mit injizierbaren Leberextracten, Tung-Chi med. Monatschr. **8:** 191, 1933.
169. Vortiainen, A.: Results of Campolon Therapy of Pernicious Anemia, Duodecim (Helsingfors) **48:** 250, 1932.

Selected Abstracts

Asthma and Hay Fever

UNDER THE DIRECTION OF SAMUEL M. FEINBERG, M.D., AND THEODORE B. BERNSTEIN, M.D., CHICAGO

Observations on the Ineffectiveness of Oral Administration of Potassium Chloride in Various Forms of Allergy. Furstenberg, F. F., and Gay, L. N.: Bull. Johns Hopkins Hosp. **67:** 219, 1940.

Potassium chloride was administered to a clinic group of eighty-five patients manifesting allergic symptoms. Of this number, fifty complained of pollen hay fever; seventeen had perennial allergic rhinitis; three had rhinitis due to physical factors; six had chronic angioneurotic edema and urticaria; four had eczema; and five complained of asthma. The potassium chloride was given in tablet, powder, capsule, and liquid form. The daily dosage varied from 15 to 80 grains. Most patients received the medication for one week, and a few for as long as one month. The results were uniformly poor, and no appreciable therapeutic benefit was obtained. A few patients who thought they received relief from the salt derived equal comfort when, unknown to them, sucrose was substituted. A number of the grass hay fever patients improved concomitantly with the drop of the atmospheric pollen count.

Potassium Chloride in Allergy. Smith, F., and Steffensen, W. H.: J. Michigan M. Soc. **39:** 485, 1940.

The authors treated a series of 117 patients with allergic rhinitis or allied disorders and obtained results characterized as "amazing." The therapy consisted of 10 grains of potassium chloride in a full glass of water three times daily, after meals. In a number of cases, the dose was increased to 50 or 60 grains daily. Of the twenty-six hay fever patients treated throughout the season, nine were completely relieved and fifteen were improved. Seventeen patients with food allergy were treated; five obtained complete relief and nine were improved. In a group of fifty-one patients with mixed allergy, seven were completely relieved and thirty-two were improved. One patient experienced complete relief and nine were improved in a group of eighteen persons whose symptoms were allergic, but in whom the symptom-producing allergens had not been identified.

Flora and Pollen Surveys of Seattle and Vicinity. Stroh, J. E.: Northwest Med. **39:** 258, 1940.

Stroh presents data and graphs showing the prevalence of flora in the Seattle area, their pollination dates, and their relative importance as a cause of inhalant allergy. Trees begin pollinating by February 1, but the season's peak is not reached until the middle of March. Most of the symptoms are caused by the pollen of the alder, which produces a considerable amount of potent pollen. The next worse offender is the birch (*Betula pendula*), which pollinates during April. The other trees are not considered as serious offenders. The grasses are pollinating by April, but the true season begins about May 15, reaches its height in the early part of June, and fades about July 15, with some grasses pollinating in small quantity until October. Of the many grasses, the most important from the standpoint of

concentration and potency of pollen are the blue grasses (*Poa annua, Poa pratensis, Poa compressa,* and *Poa trivialis*), orchard grass (*Dactylis glomerata*), timothy (*Phleum pratense*) and perennial rye (*Lolium perenne*). English plantain (*Plantago lanceolata*) pollinates through the grass season until late fall and is an important offender, as is also velvet grass (*Holcus lanatus*). The weed pollens are of minor importance; those weeds which grow in the vicinity are not abundant or widely distributed, and their pollens rarely give reactions. However lamb's-quarter (*Chenopodium album*), pigweed (*Amaranthus retroflexus*), and mugwort give strong reactions at times and can be serious offenders. The ferns shed an abundance of pollen, but the author states he has never seen a true case of fern spore hay fever. Mold spore counts are small; those identified were species of *Alternaria, Hormodendrum, Aspergillus, Cephalosporium, Mucor, Monilia, Penicillium, Rhizopus, Trichoderma,* and *Fusarium.*

Hay Fever: The Value of Daily Atmospheric Counts of Pollen Grains and Mold Spores in Diagnosis and Treatment. Hansel, F. K.: J. Missouri M. A. 37: 241, 1940.

Hansel discusses the meteorologic variations which influence the daily variations in the concentration of pollen in the air, and the importance of daily determinations of pollen grains and mold spores in the diagnosis and treatment of hay fever. Graphs showing the amount of tree, grass, and ragweed pollen in the air during the 1939 season in St. Louis are presented. *Alternaria* spores were found to constitute 34 per cent, *Hormodendrum* spores, 24 per cent, *Helminthosporium* spores, 3 per cent, and rusts and smuts, 39 per cent, of the spores of fungi which could be identified on the slides. Since many ragweed patients are also sensitive to molds, the author has obtained much more satisfactory results when he has treated these patients with extracts of molds, in addition to the regular ragweed extracts. Food sensitivities also must be watched for during the hay fever season, and food avoidance practiced.

Garlic: An Occupational Factor in the Etiology of Bronchial Asthma. Case Report. Henson, G. E.: J. Florida M. A. **27**: 80, 1940.

A case is reported of a young male with ragweed hay fever who developed a return of hay fever symptoms late in September, 1938. The symptoms continued, and finally asthma appeared, attacks of which occurred every day and interfered with work and sleep. Reactions upon retesting were negative to all the proteins except garlic and ragweed pollen. The patient worked in a sausage factory where powdered garlic was used profusely. The kernel of garlic was substituted for the powdered form. Within two days he became entirely free of asthma, and this cessation of symptoms has lasted now for more than seventeen months.

Dermatology

UNDER THE DIRECTION OF MARION SULZBERGER, M.D., NEW YORK, AND JOSEPH GOODMAN, M.D., BOSTON

Experiments With Histaminase. Simon, F. A.: J. Invest. Dermat. 3: 299, 1940.

By injecting histaminase solution intradermally in five locations in a normal person, and following it with histamine immediately, five minutes later, one hour later, and twenty-four hours later (the fifth site being a control), it was demonstrated that histaminase was not capable of abolishing the action of histamine under these circumstances. The reverse of this experiment demonstrated that the

injection of histaminase into a histamine wheal would not abolish the reaction. Likewise it was found that histaminase was not capable of destroying the "H-substance" of hay fever. Moreover, the administration of histaminase for a week was found to have no effect upon the nasal symptoms following an experimental exposure of a sensitive person to ragweed pollen. Also, no effect of histaminase could be demonstrated on the wheals of a patient with dermographism.

Experiments in Poison Ivy Sensitivity. Effects of Specific Injections on the Level of Sensitivity to Quantitative Patch Tests and on Clinical Sensitivity. Greenberg, S., and Mallozzi, E. D.: Arch. Dermat. & Syph. **42**: 290, 1940.

This paper reports the results of studies of more than 300 adult men engaged in outdoor work, mostly in areas where there was a moderately heavy growth of poison ivy. A group of 278 men was tested with serial dilutions of the extract (from full strength to 1:100,000). Of those tested, 159 had no reactions whatsoever. The remaining 119, who showed reactions, were divided into two groups. The first group was given two intramuscular injections of the poison ivy extract (seventy-seven persons). The second group was given injections of the vehicle of the extract (forty-two persons). Six weeks after the injections, the 159 men were retested with quantitative serial dilutions of the extract as in the first set of tests. No reduction of sensitivity could be demonstrated in that group which received the specific injections. There was considerable fluctuation of the degree of sensitivity in both groups.

Poison ivy dermatitis developed in 27 per cent of the group which received the injections of extract and in 36 per cent of the group which received the control injections.

A Histochemical Study of Neurodermatitis. Preliminary Report: Microincineration and Spectrographic Analysis. Engman, M. F., and MacCardle, R. C.: Arch. Dermat. & Syph. **42**: 109, 1940.

By the methods mentioned in the title the authors believe that they have demonstrated a general change in the skin of patients with atopic dermatitis. The most marked element of change is a decrease in magnesium content.

These conclusions are based on a study of sixty-three biopsy specimens from persons with normal skin, and of biopsies of normal and diseased skin taken from twenty-four patients with atopic dermatitis.

Relapsing Early Acute Arsenical Erythema: Report of Two Cases. Thomas, E. W., and Cañizares, O.: Arch. Dermat. & Syph. **42**: 30, 1940.

The early, acute, arsenical erythemas usually do not recur if an arsenical is administered after recovery. The authors have reported two exceptional cases in which there were recurrences. In one instance there were flares of the eruption after each of several trial injections of mapharsen, given over a period of several months. Eventually, however, this patient tolerated mapharsen once more. The second patient had one recurrence of the eruption. Subsequently the drug which originally caused the eruption was well tolerated.

Exfoliative Dermatitis Due to Naphthalene. Report of an Eruption Resembling Mycosis Fungoides. Fanburg, S. J.: Arch. Dermat. & Syph. **42**: 53, 1940.

The patient reported on presented the picture described by Sulzberger and Garbe ("Distinctive Exudative Discoid and Lichenoid Chronic Dermatosis") and by Cannon ("Allergic Dermatitis Simulating Lymphoblastoma"). Recurrence

was prompt on each return home from a hospital stay. Eventually recurrences were traced to exposure to naphthalene (moth flakes). Since that time (seven years ago) the patient has remained well.

Clinically the eruption suggested mycosis fungoides. Several biopsies were performed during the course of the illness. Two competent dermatopathologists found a microscopic picture which strongly suggested mycosis fungoides.

Immunology

UNDER THE DIRECTION OF MATTHEW WALZER, M.D., AND MAX HARTEN, M.D., BROOKLYN

In Vitro Anaphylaxis in the Surviving Intestine. Nicoll, P. A., and Campbell, D. H.: J. Immunol. **39:** 89, 1940.

The authors report on the advantages of using surviving smooth muscle (guinea pig intestine) for studying the mechanism of anaphylactic shock and as a test for sensitivity.

Guinea pigs actively sensitized with ovalbumin were used. Three segments, suspended in a bath of slightly modified Tyrode solution with the pH controlled, were used simultaneously in the majority of the experiments. The most satisfactory intestinal strip was a longitudinal segment of ileum about 3 cm. long. Rings or strips of circular muscle from the small intestine and preparations from the esophagus or stomach were unsatisfactory. Preparations from the ascending colon and cecum also gave satisfactory response. Strips stored in the icebox at 5° C. could be tested for sensitivity many hours after removal from the animal.

Under the conditions employed for sensitization in these experiments, the isolated intestinal strips did not respond to stimulation until after the sixth day following the sensitizing dose. A relationship was shown to exist between the degree of sensitivity and the antigen concentration used for the in vitro test.

The nature of the response when the animal was sensitized to two antigens was shown to depend upon the order of testing. When the stronger antigen was tested first, the response to the second antigen was definitely weaker than when the reverse order was followed.

Ileac segments obtained from passively sensitized animals responded as well as did those from actively sensitized animals.

Surviving intestinal segments from sensitized guinea pigs proved to be as reliable as the virgin uterus in testing by the Dale Method.

Anaphylactic Shock and Susceptibility to Histamine Poisoning in the Cotton Rat (Sigmodon Hispidus Littoralis). Seegal, B. C.: Proc. Soc. Exper. Biol. & Med. **44:** 628, 1940.

The author reports attempts at producing anaphylactic shock in the Florida cotton rat.

Cotton rats were given one or two injections of sheep serum or whole egg white and were then tested intravenously after an incubation period of from seventeen to twenty-nine days. In no case was any reaction obtained following the shocking injection of the sheep serum. Six of these eight animals, when retested seventeen days later, still gave negative results. In one of nine animals sensitized with whole egg white, autopsy findings suggested the picture of anaphylaxis.

Precipitin studies made from nineteen to twenty-three days after the last test injection of sheep serum revealed no precipitins in three of the five animals studied.

In one serum a trace of antibody was evident with antigen diluted 1:20; in another serum definite precipitate could be observed with antigen diluted 1:640. Precipitin studies in four of the nine animals sensitized with egg white revealed a trace of precipitate in one animal when tested with antigen diluted 1:100.

The minimum lethal dose of histamine administered intravenously was approximately 0.8 mg. per 100 Gm. for the cotton rat. This is fifteen times the quantity required to kill a guinea pig, but is one hundred times less than that which has been reported lethal for the rat.

Evaluation of the Tuberculin Patch Test. Fineman, A. H., and Bair, G.: Am. J. Dis. Child. **60**: 631, 1940.

Three hundred and thirty children, ranging in age from 4 months to 14 years, were studied in order to determine the reliability of the patch test with tuberculin as compared with the Pirquet and Mantoux tests.

The Pirquet test was performed first. If it was negative, the tuberculin patch test and the Mantoux test (0.1 mg. O. T.) were performed simultaneously forty-eight hours later on the upper and inner part of the same forearm. Readings were made at forty-eight hours and as late as from four to seven days after the test.

Results of the Pirquet and patch tests agreed in 313 patients, or 95 per cent, and disagreed in seventeen, or 5 per cent. Of these seventeen patients, fourteen were positive to the patch test and negative to the Pirquet test. Eleven of these fourteen patients showed positive reactions to the Mantoux test. Results of the patch and Mantoux tests agreed in 278 patients, or 97 per cent, and disagreed in nine, or three per cent. Six of these nine patients reacted negatively to the patch test and positively to the Mantoux test. Three children showed positive reactions to the patch test and negative reactions to the Mantoux test. In some instances a faint erythema or negative reaction to the patch test at forty-eight hours became definitely positive at ninety-six hours.

The authors conclude that the tuberculin patch test is simple, practical, and reliable, and is somewhat more sensitive than the Pirquet test and slightly less sensitive than the Mantoux. For routine work, the patch test is recommended as the initial test in place of the Pirquet. If it is negative at the end of one week, a Mantoux test with 0.1 mg. O. T. is advised.

Pediatrics

UNDER THE DIRECTION OF WILLIAM C. DEAMER, M.D., SAN FRANCISCO

Asthma in Childhood: A Discussion of the Psychological Aspect. Hall, M. B.: Brit. M. J. **2**: 1028, 1940.

After reviewing the literature on the psychologic aspects of asthma, the author illustrates the subject with five case reports dealing with children. In each instance the patient was referred by another physician for psychologic investigation. Treatment of a psychologic nature was directed at the parents as well as the patient. All patients were well above average intelligence and had personality traits which have been described as occurring in the allergic group. The five patients improved under treatment, and no other form of therapy was used during the time they were under observation. The children were from 9 to 15 years of age, and a family history of allergy was present in each instance. The desirability of employing psychologic methods of treatment in selected cases of asthma is stressed.

Allergy in Children. Chown, G.: Canad. M. A. J. **43**: 141, 1940.

The author discusses in a general way the subject of allergy in childhood and includes five brief case reports. He believes the psychic factors in childhood are much less evident than they are in adult allergic disease. Skin tests have not helped him in treating infantile eczema, nor has evaporated milk proved very useful. Elimination diets are extremely difficult to carry out and are little used. Food allergy is thought to play a more important role than inhalants in patients of the pre-school age, whereas later in life the reverse is true.

Hospital Mortality and Morbidity of Infantile Eczema. Glaser, J., and Edwards, W. M.: Am. J. Dis. Child. **60**: 527, 1940.

The authors had the impression that, in comparison with published reports, especially those of Koch and Schwartz, the mortality of their hospitalized cases of infantile eczema was relatively low. This was borne out by their finding a mortality of 3.8 per cent for infants with eczema admitted to three Rochester hospitals, whereas Koch and Schwartz reported a 14.4 per cent mortality in Milwaukee.

One hundred and six cases comprise the authors' series. Four deaths occurred, and in each, some complication was present on entry to the hospital. In the forty-five cases in which no complication was present on entry, no deaths occurred. In the latter group, however, complications developed in 31 per cent after admission to the hospital.

The most common complications were of a respiratory and gastrointestinal nature. It is suggested that this is not merely a coincidence, but possibly may be explained on the basis of similarity in evolution and function of these two systems and the skin. It is pointed out that they all present surfaces where the individual is in contact with his environment.

Despite their relatively favorable experience, the authors advise caring for an infant with eczema outside of an institution whenever possible.

On the Diagnosis and Therapy of Bronchial Asthma in Childhood. Frick, P.: Monatschr. f. Kinderh. **77**: 421, 1939.

The author outlines the usual approach which he uses in working out the problem of childhood asthma. This resembles that detailed by most American authors, but not seen in practice in Europe as frequently as in this country. It includes group testing by the intracutaneous method, with the use of several antigens in one mixture. The members of the group with positive reactions are, of course, tested individually. The results of tests are considered less important than the history and are to be interpreted in the light of the history.

Environmental allergens are of greater importance than food allergens, save in eczema. A change of environment is used frequently to initiate improvement pending alterations in the home. Desensitization is considered only in association with elimination of offending antigens, and of the two approaches to the problem, it is decidedly the less important.

Bacterial allergy, with delayed reactions appearing in from eight to twenty-four hours, occurs in certain cases, especially those ushered in by infections such as measles, grippe, and whooping cough.

The Value of Dextrose in Bronchial Asthma in Children. Prince, A.: New York State J. Med. **40**: 1385, 1940.

The author is enthusiastic over the results of using dextrose by mouth in the prevention and treatment of asthma. Every one of five cases responded dramatically to this simple and inexpensive form of treatment, he claims. The treatment calls

for taking several spoonfuls of dextrose by mouth frequently during the day. Other sugars do not afford the same relief. Fasting blood sugar values of from 54 to 90 mg. per cent, some of them taken during an attack, are interpreted as further indication that hypoglycemia is a major factor in the production of attacks. The method of determining the blood sugar is not given, nor are fasting values after the daily use of dextrose reported.

Allergic Intestinal Bleeding in the Newborn: A Clinical Syndrome. Rubin, M. I.: Am. J. M. Sc. **200:** 385, 1940.

Four instances of what appears to be allergic melena are described. In each case a strong family history of allergy was present. Cow's milk was started within a few days after birth in all four patients, and within from three to five weeks, blood appeared in the stool, accompanied by colic, unusual hunger, or gastric peristaltic waves. The amount of blood varied from small, pinhead-sized clots mixed with stool to frank hemorrhage with no fecal matter. Mucus was usually present, and in one instance eosinophiles were demonstrated in the mucus.

Other causes of hemorrhage were considered to have been ruled out, and all the patients were relieved of bleeding and other symptoms within forty-eight hours after the omission of cow's milk. Goat's milk was well tolerated by all patients save one, in whom within three weeks, it too appeared to cause bleeding. A second trial of cow's milk in one patient caused the bleeding and associated symptoms to reappear. Three of the four infants subsequently developed eczema, and one developed asthma.

Intracutaneous tests were negative to cow's milk. Because goat's milk caused improvement, the lactalbumin fraction of cow's milk was blamed. Because of the rapid disappearance of symptoms in every instance in which cow's milk was withdrawn, the author considers a purely local, rather than a general, allergic reaction to be responsible.

Rhinology and Ophthalmology

UNDER THE DIRECTION OF FRENCH K. HANSEL, M.D., ST. LOUIS

Allergy of the Upper and Lower Respiratory Tracts in Children. Hansel, F. K.: Ann. Otol., Rhin. & Laryng. **49:** 579, 1940.

In an analysis of 455 cases studied in the Pediatric Allergy Clinic of Washington University, the incidence of various types of respiratory allergy was tabulated. It is noteworthy that the incidence of pure nasal allergy is only about 15 per cent; this could be accounted for, however, by the fact that diagnosis was frequently missed in cases of this type. It was pointed out that many patients who had respiratory allergy and not infection were subjected to tonsillectomy for relief of colds and bronchitis. A new technique of staining nasal and bronchial secretion which requires only about one to one and one-half minutes is described. A great deal of space is devoted to the matter of interpretation of cytologic pictures. A number of case reports are presented which illustrate the value of cytologic studies in diagnosis and in the determination of the clinical course of respiratory allergy in its relation to complicating infection.

The Importance to the Internist of Latent Paranasal Sinusitis. Lathrope, G. H., Peer, L. A., and Paddock, R.: Ann. Int. Med. **12:** 1576, 1939.

Lathrope, Peer, and Paddock state that in latent sinusitis there are few local symptoms, yet the hyperplastic mucous membrane can be demonstrated readily by the use of contrast media. They further state that, although the irrigation fluid may

fail to reveal them, bacteria may still be present in the deeper layers of the thickened membrane, their toxic products being continually absorbed, causing constitutional symptoms. In a series of 100 cases of chronic disease of the antrum, suppurative in fifty and hyperplastic in forty-nine, the chief subjective symptoms were: lassitude, eighty-two; repeated colds, sixty-three; rheumatic pains, fifty; cough, thirty-six; indigestion, thirty-three; loss of weight, twenty-three; asthma, fourteen; and hay fever, eight. It is very probable that in the twenty-two cases of hay fever and asthma the pathologic changes in the sinus were primarily of allergic origin. It is also very probable that among those patients with repeated colds there were also a significant number with nasal allergy. Allergy, as such, was not considered an important factor in the 100 cases of chronic disease.

Le radio-diagnostic des affections allergiques du nez et des sinus. Thienpont, R.: Bull. Soc. belge d'otol., rhinol., laryng. p. 32, 1939.

Thienpont emphasizes the fact that allergy influences the interpretation of roentgenologic films. Whenever the routine roentgenologic and clinical examinations are inconclusive, he advises further studies with iodized poppy-seed oil, plus a determination of the emptying time. He found that ciliary activity in the sinuses remains almost normal despite extensive polyposis of allergic origin, whereas it is markedly impeded if the pathologic condition is truly infective.

The Value of Roentgen Examination of the Paranasal Sinuses. Johnson, V. C.: Radiology **32**: 303, 1939.

Johnson reports the results of an analysis of 854 successive roentgenologic examinations of the sinuses in cases in which the clinical records were complete. The comparison of the roentgenologic with the clinical diagnosis shows a close parallel, the former being positive in 632 cases, the latter in 614. The agreement between the two was positive in 539 and negative in 140, a total of 679, or 80 per cent of the entire group. Pathologic changes were found in 131 of 133 cases subjected to surgical interference. The clinical and roentgenologic diagnoses were in agreement in 128 of these. An analysis of the findings in 163 sinuses which were operated upon and in which simple clouding was reported in preoperative roentgenologic study revealed that the most frequent findings were pus in thirty-three, and pus and thickened membrane in sixty-seven. In thirty-seven sinuses operated upon, which showed thickened membrane by x-ray examination, there was pus in thirteen, and pus and thickened membrane in fifteen. There is no correlation of allergic studies to determine the possible incidence of allergy among those patients in whom thickened membranes were found.

Les relations entre les polypes du nez et les affections des cavités paranasales. Podvinec, S.: Ann. d'oto-laryng. p. 266, March, 1939.

Podvinec has shown that nasal polyps usually arise from locations in the lateral nasal wall where there is duplication of the mucous membrane, such as the lips of the hiatus semilunaris, the maxillary ostium, and the ostium of the individual ethmoid cells. Numerous drawings demonstrate the acute angle formed by the margins where the mucosa lies in two layers back to back. These sites of predilection for the development of polyps were described by Zuckerkandl more than fifty years ago. Histologically, the mucosa in the region of the ostia of the various sinuses is comparatively thinner and much more delicate than that of other parts of the nasal cavities. As a matter of fact, the tissue in these areas has a loose, myxomatous-like stroma which readily undergoes extensive edema, with resultant polypoid formation. The polyps were very rare on the septal surface of the middle turbinate, the inferior turbinate, or the septum; when they do occur in these areas, they are usually papillomatous and are not the true edematous type of polyp.